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PROBLEM DEFINITION STUDIES ON POTENTIAL ENVIRONMENTAL POLLUTANTS

IV. PHYSICAL, CHEMICAL, TOXICOLOGICAL, AND BIOLOGICAL PROPERTIES OF BENZENE; TOLUENE; XYLENES; AND *p*-CHLOROPHENYL METHYL SULFIDE, SULFOXIDE, AND SULFONE

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This report establishes a data base of physical, chemical, toxicological, and biological properties for: benzene, toluene, xylenes, and p-chlorophenyl methyl sulfide, p-chlorophenyl methyl sulfoxide, and p-chlorophenyl methyl sulfone; and provides a summary of pertinent information concerning: physical/chemical properties; analytical methods; mammalian toxicology; environmental considerations for wildlife, birds, fish, reptiles, amphibians, invertebrates, microorganisms, and plants; and existing standards.

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Volatilization
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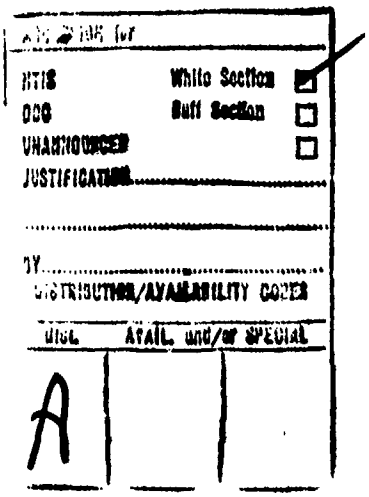
Xylenes

PREFACE

This problem definition study was completed for the DA Project Manager for Chemical Demilitarization and Installation Restoration (PMCDIR) by a team organized at the U.S. Army Medical Bioengineering Research and Development Laboratory (USAMBRDL). The team consisted of members of the professional staff of the Environmental Protection Research Division (EPRD), USAMBRDL, and professional consultants from Walden Research Division (WRD) of Abcor, Incorporated. Individuals who contributed professionally to the preparation of this report are shown in a subsequent list of contributors.

The authors acknowledge the following individuals who supported this effort and made the preparation and publication of this report possible: LTC L.H. Reuter and MAJ I. Muul, EPRD, USAMBRDL; Mr. K.W. Ferree, Mrs. L.E. Edwards and Mr. D. Grant, technical information specialist, WRD; CPT D.E. Shackelford, Mrs. J.M. Arkins, Mrs. E.M. Snyder and Mrs. M.F. Bostian of the Administrative Support Division, USAMBRDL; Dr. D.L. Crawford, microbiologist and Dr. E.C. DeFabo, Plant Physiologist, WRD; Mrs. D. Ranum and Mrs. L. Deem, WRD; Dr. R.S. Valentine, Mr. R.E. Snyder and Ms. M. Tonkin of Atlantic Research Corporation; and Mr. L.L. Ware, Jr. and Ms. D.C. Daymont of the Scientific and Technical Information Office, U.S. Army Medical Research & Development Command.



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INTRODUCTION

An earlier report in this series[1] assessed the toxicological and ecological hazards of benzene, toluene, xylenes,* and *p*-chlorophenyl methyl sulfide, sulfoxide, and sulfone at Rocky Mountain Arsenal (RMA). That assessment included a discussion of the occurrence of these substances at RMA and their anticipated behavior in that milieu; the calculation of preliminary Soil Pollutant Limit Values (SPLV's) for those substances about which sufficient information was available; and the identification of information voids and recommendations for research to supply information needed to adequately assess adverse health and environmental effects. The organization of technical and professional personnel, the manual and computerized literature searches, and the information handling system used in this problem definition study have been detailed in the initial report of this series.[2]

OBJECTIVE

The objective of this study is to provide technical information on the physical, chemical, toxicological, and biological properties of benzene, toluene, xylenes, and *p*-chlorophenyl methyl sulfide, sulfoxide, and sulfone.

SUMMARY OF FINDINGS

The findings from this study are presented in detail for each substance in Appendixes A through D. Pertinent information concerning physical/chemical properties, analytical methods, mammalian toxicology, environmental considerations, and standards has been extracted from the appendixes and is summarized below.

PHYSICAL/CHEMICAL PROPERTIES

All of the compounds studied are of relatively low water solubility and high solubility in many organic media. They are therefore extractable into water-immiscible solvents. They range, as evidenced by the boiling points, from relatively volatile (benzene) to relatively non-volatile (*p*-chlorophenyl methyl sulfone). There is little evidence to indicate non-biological degradation of these compounds in the absence of light. If such reactions occur, they most likely would be air oxidation of the sulfide to sulfoxide and thence to sulfone. There is qualitative evidence for atmospheric photochemical degradation of the solvents,

* The term xylene, in the singular, refers to any undefined mixture of *o*-, *m*-, and *p*-xylene.

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but no quantitative data. References have been given for synthesis of those compounds (especially the sulfoxide) that may not be commercially available. Adequate references were located for spectrochemical characterization, e.g., by infrared, ultraviolet, nuclear magnetic resonance and (in some cases) mass spectra. Information relevant to the subsurface transport of these compounds is almost completely lacking. Accounts of biochemical transformations were found for the solvents, but generally not for the sulfur compounds, except that mouse liver and house fly microsomes convert the sulfide to the sulfoxide.

ANALYTICAL METHODS

All of the compounds discussed here are best analyzed at low levels by gas-liquid chromatography. For the sulfur compounds, a sulfur-specific flame photometric detector gives the most sensitive response.

MAMMALIAN TOXICOLOGY

Benzene exhibits appreciable toxicity beyond the narcotic properties common to the three solvents. Air concentrations ≥ 200 ppm produce some narcotic effects and are slightly irritant to mucous membranes, with xylene being slightly more irritant than benzene or toluene. Benzene, however, produces bone marrow damage with consequent reduction in red blood cell counts and changes in the differential white blood cell counts. While these changes tend to revert to normal in most instances, a small percent of those exposed go on to develop aplastic anemia and/or leukemia, eventually resulting in death.

The acute oral and dermal LD_{50} have been determined for p-chlorophenyl methyl sulfide, sulfoxide and sulfone. The data would indicate that these compounds are not very toxic to mice. However, the sulfoxide produced some skin reactions on rabbits. No other toxicological studies have been reported.

ENVIRONMENTAL CONSIDERATIONS

Benzene. Benzene can be removed from the soil by volatilization and is degraded by microbes. Its half-life in soil is less than 1 month, although its persistence probably depends on soil type and climatic factors. Benzene is slightly soluble in water. Bacterial degradation of benzene usually proceeds via dihydroxylation to catechol, followed by ring cleavage, in the presence of molecular oxygen, and degradation to CO_2 and water. Anaerobic degradation is little studied, but proceeds more slowly than aerobic metabolism. Benzene is relatively toxic to fishes, the 96-hour LC_{50} ranging from 9.57 to 45 mg/l for adults, larvae and eggs. Sublethal concentrations increase respiratory rates and have been implicated in the production of tumors. Benzene, or its metabolites, may be present in the skeletal muscle of contaminated fish. Benzene is toxic to insects. High concentrations of benzene are toxic to those microorganisms which can normally metabolize it. Sublethal amounts elicit negative chemotaxis from some microbes.

Benzene is lethal to plants at high concentrations (>6.4 x 10^{-4} M/l of air) and at short (30 min) exposure times. Lower concentrations are less toxic, and recovery from sublethal effects is possible in all plant species studied. Carrots, and other Umbelliferae, are less susceptible to the toxic effects. Plant growth and rooting is stimulated by aqueous solutions containing low benzene concentrations (0.01-0.1 saturated). Aqueous solutions containing higher concentrations (0.1-0.15% benzene) inhibit growth and interfere with metabolism and cell division. Benzene is translocated and metabolized by plants, but bioaccumulation probably does not occur.

There is no conclusive information concerning the effects or transport of benzene in the food chain. However, since such organisms as mammals, fish and plants metabolize sublethal amounts of benzene, it is unlikely that any accumulation of benzene occurs between trophic levels.

Toluene. Toluene is degraded by soil microbes and volatilizes readily. It is reasonable to expect rapid removal of small amounts of toluene from the soil. Toluene is moderately toxic to fish the 96-hour LC_{50} ranging from 22.80 to 59.30 ppm. Toxicity may progressively increase with length of exposure. Toluene is associated with the incidence of tumors in fish and may be present in the muscle and liver of contaminated fish, including eels. The noxious odor of toluene-contaminated fish is not removed by cooking. Toluene is toxic to insects and nematodes. Toluene is metabolized by some microbes, but is toxic to methane-producing bacteria at 200 mg/l.

Toluene is lethal to barley plants at high concentrations (4.9 x 10^{-4} mol/l of air) and at short (30 min) exposure time. Lower concentrations are less toxic, and recovery from sublethal effects is possible in all plant species studied. Carrots, and other Umbelliferae, are less susceptible to the toxic effects. Plant rooting is stimulated by aqueous solutions containing low toluene concentrations (0.01-0.1 saturated). Toluene is metabolized by the fruits of several plants, but bioaccumulation probably does not occur.

There is no conclusive information concerning the effects or transport of toluene in the food chain.

Xylene. Xylene can be degraded by soil microbes. It is sparingly soluble in water and has an estimated half-life in soil of 1 to 6 months. Xylene from dietary sources accumulates in the skeletal muscle of pigs, but is cleared after termination of exposure. It is teratogenic and lethal to chicken embryos. It is moderately toxic to fish, the 96-hour LC_{50} values range from 16.94 to 36.81 mg/l, and can accumulate in the skeletal muscle. Some fish avoid xylene concentrations as low as 0.1 ng/l. Xylene is toxic to insects. Saturation levels of xylene are toxic to Nocardia spp.

Xylene is lethal to young barley plants at high concentrations (2.4×10^{-4} M/l of air) and at short (1 hour) exposure times. Lower concentrations for shorter length of exposure are less toxic, and all plant species tested were able to recover from sublethal effects. Carrots, and other Umbelliferae, are less susceptible. Plant rooting is stimulated by aqueous solutions containing xylene at concentrations of 0.01-0.1 saturation. Germination of seeds of some plants is retarded. Xylene at 100 ppm is effective for the elimination of waterweed. There is no evidence that xylene is bioaccumulated or metabolized by plants.

There is no evidence to suggest that xylene is bioconcentrated between trophic levels. In fact, the noxious odor of xylene-contaminated prey could deter predation.

p-Chlorophenyl Methyl Sulfide, Sulfoxide, and Sulfone. There are indications that these compounds are phytotoxic to grasses. Other consequences of their presence in the environment are unknown.

STANDARDS

The National Institute of Occupational Safety and Health (NIOSH) has recently reviewed the occupational hazard associated with the use of benzene, toluene, and xylene and has recommended the following limits in workroom air for a 40 hour work week:

Solvent	Time Weighted Average (TWA)		Ceiling Value	
	ppm	mg/m^3	ppm	mg/m^3
Benzene	10	32	25	80
Toluene	100	377	200	754
Xylene	100	434	200	868

The TLV's have been superseded by the above TWA values. There are no standards for the p-chlorophenyl methyl sulfur compounds.

LITERATURE CITED

1. Miller, T.A., D.H. Rosenblatt, J.C. Dacre, D.R. Cogley and J.L. Welch (eds.), "Problem Definition Studies on Potential Environmental Pollutants. III. Toxicology and Ecological Hazards of Benzene; Toluene; Xylenes; and p-Chlorophenyl Methyl Sulfide, Sulfoxide, and Sulfone at Rocky Mountain Arsenal," Technical Report 7604, U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, MD (June 1976).

2. Rosenblatt, D.H., T.A. Miller, J.C. Dacre, I. Muul and D.R. Cogley (eds.), "Problem Definition Studies on Potential Environmental Pollutants. I. Toxicology and Ecological Hazards of 16 Substances at Rocky Mountain Arsenal," Technical Report 7508, U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, MD (December 1975).

APPENDIX A

BENZENE

ALTERNATIVE NAMES

Benzol; cyclohexatriene; phenyl hydride

PHYSICAL AND CHEMICAL PROPERTIES[1-3]

Basic Physico-Chemical Information

CAS Reg. No.: 71-43-2

Toxic Substances List: CY14000

Wiswesser Line Notation: RH

Molecular formula: C_6H_6

Molecular weight: 78.11

Conversion factors (air, 25°C): 1 ppm = 3.19 mg m^{-3}; 1 mg m^{-3} = 0.313 ppm

Freezing point: 5.506°C

Boiling point: 80.103°C

Density: 0.87368 at 25°C

Refractive index: n_D = 1.49790 at 25°C

Vapor pressure:[2] $\log_{10} P = 6.89745 - [1206.350 / (220.237 + t)]$ where P is vapor pressure in mm of mercury and t is temperature in °C. (Thus, the vapor pressure at 25.1°C is 100 mm.)

Solubility in water: In the range of 10° to 25°C, the solubility of benzene is nearly constant, i.e., 0.173% according to Arnold, et al.;[4] the data fit the following equation from 0.4° to 69°C (where T is in °C):

$$S \text{ (in \% solubility)} = 0.1784 - 7.436\times10^{-4}\, T + 1.906\times10^{-5}\, T^2 + 1.217\times10^{-7}\, T^3$$

Determinations by Brown and Wasik of the National Bureau of Standards[5] (0.179% at 17.9° and 0.176% at 20.1°) and by other authors[6-8] essentially

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agree with these figures. Other stated aqueous concentrations of benzene, mentioned elsewhere in this Appendix in regard to testing of biological effects of benzene, are quoted as stated by the researchers, even though these appear to exceed the solubility of benzene.

Solubility in organic solvents: Miscible with alcohols and others; soluble in most organic solvents.

Partition coefficient between vapor and water: 5.51 at 20.6°C[5] where K_p = Conc. in liq./conc. in vapor

Partition coefficients between the aqueous phase and immiscible organic solvent layers have been investigated only infrequently.[6,9-12] Typical values for K_d (K_d = Conc. in organic phase/conc. in aqueous phase) are 120 for sunflower oil, 182 for *n*-heptane, and 135 for octanol.[9] The odor threshold for benzene in air is 4.7 ppm.[3] Sources of spectral data are referenced in Table A-1. Benzene is comparatively stable in air and water, and in contrast with soil, and reacts with other chemicals only under drastic conditions or with the aid of enzymes.

TABLE A-1. SOURCES OF SPECTRAL DATA FOR BENZENE

Type of Spectra	Sources of Spectral Collections	Reference Collection Number	Ref.
Infrared	Sadtler Research Laboratories, Inc. 3316 Spring Garden St., Philadelphia, PA	SADG-136	16
	Aldrich Library of IR Data	15,462-8	17
Ultraviolet	Sadtler Research Laboratories, Inc. 3316 Spring Garden St., Philadelphia, PA	SAD-198	16
Nuclear Magnetic Resonance	Sadtler Research Laboratories, Inc. 3316 Spring Garden St., Philadelphia, PA	SAD-3429	16
	Aldrich Library of NMR	--	18
Mass	John Wiley & Sons, Inc. 605 3rd Ave., New York, NY	Wiley-102	16

Photochemistry

Benzene is photoisomerized to various valence isomers, but usually only in very low yields, which depend on the reaction conditions.[3] Oxygen atoms produced by photolysis of ozone and nitrogen dioxide are capable of reacting with aromatic hydrocarbons. Thus, benzene released to the atmosphere might disappear by oxidation.[14] In the presence of nitric oxide, benzene undergoes photolysis to a variety of products, such as nitrobenzene, *o*-nitrophenol, *p*-nitrophenol, 2,4-dinitrophenol and 2,6-dinitrophenol.[15]

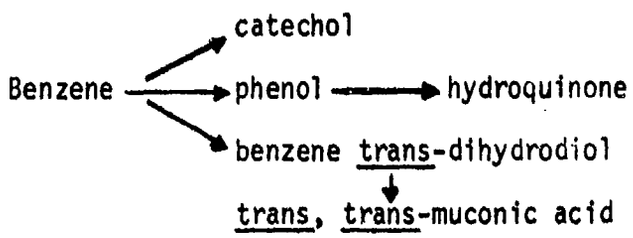
Manufacture and Uses

Benzene is obtained industrially by fractionation from light oil of coke oven gas, light oil of carburetted water gas, coal tar, and aromatic fractions from petroleum cracking and reforming. U.S. production of benzene for January and February 1976 was 222.6 million gallons, according to figures released by the U.S. International Trade Commission on April 26, 1976.

Benzene is used mainly as a raw material for the production of such chemicals as phenol, aniline, cumene, adipic acid, diphenyl, and ethylbenzene, each of which is a starting material for other products. It is also used as an antiknocking ingredient in motor fuels, and as a solvent for chemical processing, for paints and varnishes, dry-cleaning, degreasing and extraction.[1]

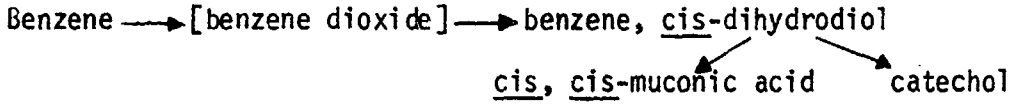
Biochemical Properties

Benzene is metabolically transformed in mammals to phenol and to a lesser extent to catechol;[19] the quantity of phenol in the urine has been used to monitor the exposure to benzene by both animals and human beings.[20] Radioactive tracer studies have shown that benzene undergoes the following series of reactions in rats:[21]



It has also been demonstrated[22] that the monooxygenase from the fungus, Cunninghamella bainieri, produces the same transformations as above. This implies the formation of a reactive intermediate, benzene epoxide (benzene oxide), which gives rise to further reactions. In the absence of the direct isolation of this intermediate, it was proved that synthetic benzene epoxide produced the same transformation as above, with the aid of liver enzymes.[22,25] Similar epoxide intermediates were actually isolated in the case of polynuclear aromatics.[26]

By contrast, Gibson and co-workers showed that the dioxygenases from the bacterium Pseudomonas putida catalyzed the oxidation of the benzene molecule by molecular oxygen, producing the following series of reactions through a dioxide intermediate.[27]



It has also been noted that benzene accelerates the action of mammalian histidine decarbonylase and plant plastid phosphatidase,[28,29] and that it reduces the oxygen affinity of deoxyhemoglobin.[30] Moreover, it has been demonstrated that plants assimilate atmospheric benzene, and cause its transformation into muconic acid, fumaric acid, succinic acid, and phenylalanine by enzymatic catalysis.[31]

Adsorption of Benzene by Natural Clay Minerals

Research on the adsorption of benzene and other solvents has not been carried out for the purposes that motivate the present problem definition study. For that reason, no data are available concerning the vapor pressure of benzene at very low benzene-to-soil loadings. The caveat must, therefore, be added that extrapolations from known behavior to low loadings risk the possibility that in the region of interest Brunauer type III or type V behavior, i.e., concavity upwards,[32] rather than the more usual type I behavior, might apply. The complex interplay of physical structure -- the size and shape of channels, interstices and bottle-shaped regions -- of chemical characteristics, and of hydrophilicity versus hydrophobicity, magnify the uncertainty inherent in generalizing from behavior on one mineral surface to behavior on another. Microscopic as well as macroscopic heterogeneity in soil minerals is the rule, rather than the exception, for which reason the argument presented below should be considered only as a starting point for possible site-specific determinations.

The present discussion is based on the results of six investigations representing work in the Soviet Union[33-37] and Japan.[38] Most of these adsorption studies were carried out on heat-dried, heat-activated or chemically-activated minerals. Activated minerals usually have a higher capacity for non-polar substances such as benzene than the same materials before activation; this is particularly true when they have been heat-treated or vacuum-dried to drive off water. Nevertheless, data by Ezdakov[36] on air-dried minerals show that the qualitative behavior of benzene is the same with these samples as with water-free samples. In fact, without indicating whether the statement applied to all minerals studied, the author[36] states that, "The adsorption of benzene by clays dried at 18.5°C [and 52% relative humidity] is accompanied by the libera-

tion of water, which collected on the bottom of the exsiccator under the layer of benzene." Thus, clay minerals, including loess (wind-deposited soil), might hold small loadings of benzene (e.g., 1 mg of benzene/kg of soil) without generating a high enough equilibrium vapor pressure of the substance by desorption to constitute an inhalation hazard; this could be true even at common relative humidities.

Adsorption data for benzene are often presented as plots of P/P_s (abscissa) vs. loading of benzene on the adsorbent (ordinate), where P is the equilibrium vapor pressure and P_s is the saturation pressure of benzene at the temperature of concern.[5] The shape of these curves varies somewhat, but a typical (and conservative) type of plot is Figure A-1. It is of significance that the inflection point B of the curve OABC invariably lies well to the right of $P/P_s = 0.1$. (C represents the loading at saturation pressure, $P = P_s$.) Thus, the curved segment OA is hypothetically convex upwards at the pressures indicated (0.1-1.0). Benzene loadings on various minerals at $P/P_s = 0.1$ are shown in Table A-2; these values have been converted in each case to units of mg of benzene/kg of mineral. Conservatively, from these data, one would estimate a benzene loading of greater than 1000 mg/kg at $P/P_s = 0.1$. Hence, according to the above model (Fig. 1) at $P/P_s = 0.0001$ the loading would be at least 1 mg/kg. According to Miller, et al.,[39] the threshold limit concentration value of P/P_s is 0.0001 (0.01%), so that soil containing 1 mg of benzene per kg should generate less than this limiting concentration.

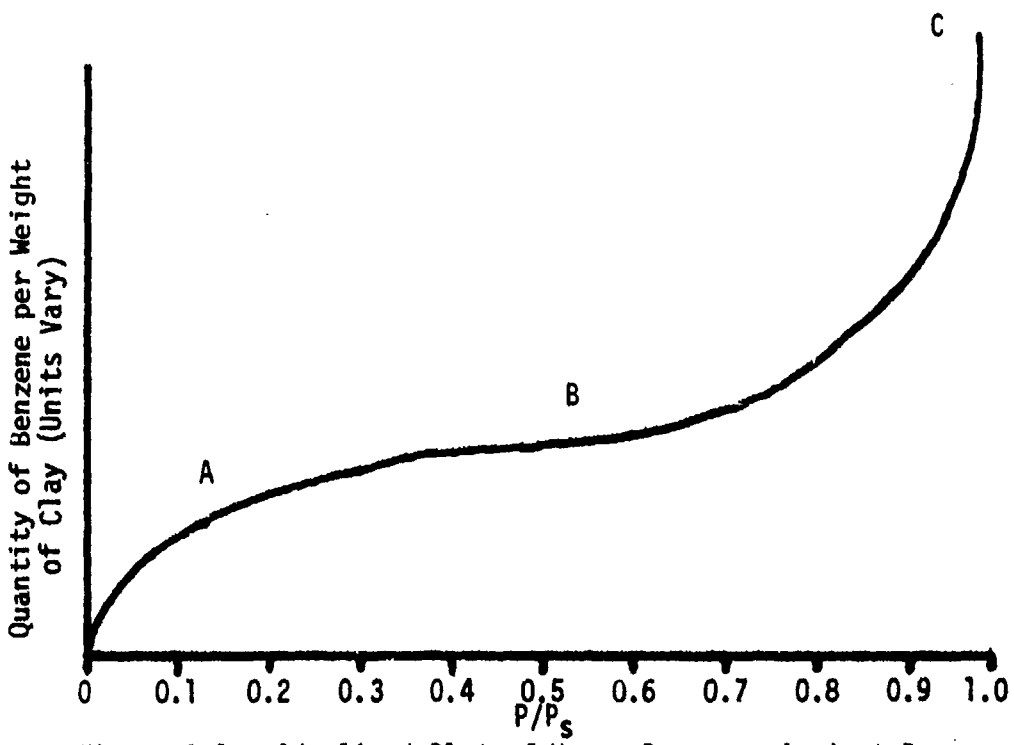


Figure A-1. Idealized Plot of Vapor Pressure Against Benzene Adsorbed on a Clay Mineral.

TABLE A-2. BENZENE LOADINGS ON CLAY MINERALS AT 0.1 SATURATION PRESSURE

Mineral	Temperature, °C	Loading, mg/kg	Reference
	Vacuum-Activated at 100°C		
Natural Askanite Clay	20	39,000	33
Activated Askanite Clay	20	101,000	33
Natural Gumbrin (bleaching clay)	20	23,000	33
Activated Gumbrin	20	39,000	33
	Vacuum-Activated at 400°C		
L-Zeolites	20	77,000 94,000	34
Compressed Silica Gel	0	110,000	38
	Vacuum-Activated at 110°C		
Glukhov Kaolinite	24	11,000	35
Palygorskite	24	25,000	35
Kvasov Hydromica	24	14,000	35
Cherkassy Hydromica	24	27,000	35
	Air-Dried, 18.5°C, 52% RH		
Loess	25	4,400	36
Hydromicaceous Clay	25	19,000	36
Bentonite	25	27,000	36
Opoka	25	19,000	36
Halloysite	25	28,000	36
Montmorillonite	25	36,000	36
	Vacuum-Activated at 150°C		
Rutile	30	2,000	37

ANALYTICAL METHODS

Benzene can be identified through use of IR, UV, NMR, or mass spectroscopy, and quantitative determinations can be made by these methods when benzene is present in reasonably large quantities. Trace amounts of benzene in air, water, soil or biomaterials are identified and analyzed by means of gas-liquid chromatography (GLC) with flame ionization detection. The details of the method of identification and estimation can be found in many references.[20,40-49] Such analysis can be applied down to 15 to 25 ppb in the sample analyzed.[50] Automatic and semiautomatic methods of GLC measurement have been worked out.[51,52]

A colorimetric method for trace quantities of benzene has been reported; it involves preconcentration on activated charcoal, extraction, oxidation by chromic acid, a second extraction with ethyl ether, and colorimetry.[53]

Silica gel, impregnated with formaldehyde and sulfuric acid, is used to indicate whether ambient concentrations of benzene exceed the limits of 50 mg/m^3 in a 6 hour period; above this limit, the indicator turns brown-red.[54]

MAMMALIAN TOXICOLOGY

The most common route of exposure to benzene is by inhalation, but absorption through the skin also occurs. The ingestion of fluids contaminated with benzene, while uncommon, is also a potential route of entry. Once exposure has taken place, excretion of unchanged benzene via the breath accounts for a third to a half of the original dose. Very little is excreted unchanged in the urine. Water soluble metabolites in the urine account for most of the remainder. These metabolites are phenol, catechol, and hydroquinone, as the ethereal sulfate or glucuronide, trans, trans-muconic acid, phenyl mercapturic acid and CO_2.[21] Very little is excreted via the feces. Since phenol is the major metabolite, and is excreted in the urine within 24 hours after exposure, urinary phenol may be used as a measure of benzene exposure.[20] A number of investigators have suggested that the phenolic metabolites are responsible for the toxic effects associated with benzene. However, the phenolic metabolites are normal urinary constituents and radioactive tracer studies indicate that they are not responsible.[55] In recent years more detailed studies have indicated that benzene is oxidized, by an enzyme or enzymes from microsomal systems, to an arene oxide which then either spontaneously or enzymatically undergoes rearrangement to phenol, a trans-dihydrodiol, and a glutathione conjugate. The reactive benzene oxide has been suggested as the immediate cause of the bone marrow toxicity that is seen in animals and man exposed to appreciable quantities of benzene.[22-24,56]

Human Exposures

Inhalation of benzene in high concentration has produced fatalities in man in a few minutes with levels as high as 66000 mg/m^3.[57-60] Lower concentrations result in an initial euphoria followed by drowsiness, fatigue, dizziness, nausea, and headache. Continued exposure may lead to convulsions, paralysis, and loss of consciousness.[58] At air concentrations above about 300 mg/m^3, but below concentrations causing any of the above symptoms, repeated or prolonged exposures have produced severe bone marrow changes, in some cases with a fatal outcome. The bone marrow changes have been variously described as aplastic anemia and leukemia.[59] Workroom concentrations approaching the TLV of 80 mg/m^3 for up to 13 years is claimed to have produced "little evidence" of benzene intoxication. Exposures to these concentrations were estimated based upon urinary phenol excretion levels. The TLV of 80 mg/m^3 seems uncomfortably close to the levels which have resulted in some fatalities in man. The odor threshold in water is cited as 31.3 ppm. The odor threshold in air is 8.8 mg/m^3, with a recognition level of about 30 mg/m^3.[61]

Benzene has been implicated as early as 1928 as a causative agent in the development of leukemia in man. A review of cases of leukemia associated with exposure to benzene reported through 1973 concludes that "a relationship between such exposure and the development of leukemia is suggested ..... ." Damage to the hematopoietic system as a result of exposure to benzene is established.[57] A contrary view regarding leukemia has been reported in 1974 as a result of an epidemiologic survey of employees of 8 European Exxon affiliated companies.[62] No abnormal occurrence of leukemia in 38,000 petroleum workers was suggested by the data. It was also noted that improvement in record keeping, job histories, exposure data and demographic data was needed. In this survey, it was found that the occurrence of aplastic anemia was so infrequent that no statistically valid calculations could be made. Eighteen cases of leukemia were found, eight in exposed and 10 in non-exposed workers. The expected numbers, based upon age specific rates in WHO data for 1966, are 6.6 and 16.7, respectively. Worker exposure was estimated to be insignificant, except for several minute long exposures to concentrations of 15 mg/m^3 or less on occasion. In 1968, in a review of the literature on benzene, Truhaut concluded that the French and U.S.A. TLV's for benzene are too high and should be reduced to 20 mg/m^3.[63] A trend in this direction in the USA is expected.[64] Another survey of 28,500 workers in the shoe, handbag and slippers industry in Istanbul for the period 1967 to 1973 turned up a total of 26 cases of leukemia and six cases of Hodgkin's disease equivalent to 13 per 100,000 over the 7 year period and 19.7/100,000 over the last 3 years. The incidence in the general population was stated as six per 100,000. Duration of exposure was 1 to 15 years, with a mean of 9.7 years. Age ranged from 16-58 years at time of diagnosis, with a mean of 34.2 years.[65] The distribution by

type of leukemia was 14 myeloblastic, four preleukemia, three erythroleukemia, three lymphoblastic, and one each of monocytic and of promyeloytic.

Chromosome aberrations in humans exposed to benzene have been reported by several investigators.[57,66-68] These are said to be non-specific and similar to those induced by X-rays. They may persist for several years after exposure ceases.[67] NIOSH, in a report prepared in 1974 on occupational exposure to benzene,[20] has analyzed the pertinent literature regarding effects in humans, including the above referenced chromosome aberrations, and was unable to determine the significance of such changes. The NIOSH report also examines the human experiences from exposures in the neighborhood of 25 ppm (80 mg/m^3) and noted that abnormal hemograms occurred in an occasional individual. Although some investigators have suggested a differing susceptibility to benzene depending upon age and sex, the preponderance of evidence reviewed in the NIOSH report does not support such differences.

Experimental Animals

The acute oral LD_{50} values for undiluted reagent grade (A.C.S., Spec.) benzene in non-fasted, Sprague-Dawley rats were: immature 14-day-old mixed sex, 3.4 ml/kg; young male adults (80-160 g), 3.8 ml/kg and mature male adults (300-470 g), 5.6 ml/kg. In this same investigation 0.0002 ml/kg is suggested as the maximum permissible limit for a single oral dose and was derived by dividing the lowest dose showing signs of biological activity by 1000. The animals were observed for 7 days following benzene administration.[69] Other investigators have reported rat oral LD_{50}'s ranging from 0.93 to 5.6 g/kg.[57] Another recent study reported an LD_{50} in male rats of 5.96 g/kg.[70] Air concentrations lethal to rats and rabbits after 30 to 100 minutes exposure are approximately 40,000 ppm.[20,57]

Rats, guinea pigs, and dogs exposed by inhalation to 817 mg/m^3, 8 hours a day, 5 days per week, for 30 repeated exposures; or to 98 mg/m^3 for 90 days or 56 mg/m^3 for 127 days (continuous 24-hour exposure) showed very little change in total white count, hemoglobin, and hematocrit. Rats, guinea pigs, dogs, and squirrel monkeys exposed to the 98 mg/m^3 (30 ppm) level also showed no changes in bromosulfalein retention, serum alanine and aspartate amino transferases, and alkaline phosphatase. Livers of the rats and guinea pigs showed no changes in tyrosine amino transferase, alkaline phosphatase and total lipids.[71] Weanling male mice, (strain C57BL/6N) after one week acclimation, were injected subcutaneously twice weekly with a 30% v/v solution of benzene in corn oil in volumes of 0.05, 0.1, 0.1, and 0.2 ml per mouse for the first 4 weeks, respectively and 0.2 ml thereafter for 40 additional weeks. Following the 44th week, injections were made once weekly through the 54th week when injections were discontinued and the mice were set aside for observation until the

104th week. The survival rate of the benzene injected animals was inferior to the controls and cases of bone marrow depletion of hemopoietic cells and hepatic necrosis were seen. However, no evidence of specific neoplasms or of total neoplasms in excess of the rates in control mice were seen.[72] This evidence of the non-neoplasia producing effect of benzene in laboratory animals is in agreement with prior studies, one of which involved skin painting in hairless mice for up to two years.[73]

Chromosome abnormalities as a result of benzene exposure (subcutaneous injection) have been observed in the bone marrow of rats.[74,75]

ENVIRONMENTAL CONSIDERATIONS

Behavior in Soil and Water

Transport: Benzene can be removed from the soil by volatilization and is degraded by microbes. Its half-life in soil is less than 1 month,[76] although its persistence probably depends on soil type and climatic factors.

Degradation. Benzene is attacked oxidatively by numerous microorganisms, especially bacteria. Bacterial degradation usually proceeds via dihydroxylation of benzene to catechol, followed by ring cleavage requiring molecular oxygen.[77] Hydroxylation may involve monooxygenase enzymes which introduce a single hydroxyl group onto the ring (e.g., converting phenol to catechol), or dioxygenases which introduce two hydroxyls producing ortho-dihydric phenols from benzene. The net result is that benzene is converted to catechol prior to ring cleavage.[77] Ring cleavage, involving the introduction of molecular oxygen between two hydroxyls, forms a non-aromatic dicarboxylic acid which can be readily degraded to CO_2 and H_2O.

Under anaerobic conditions, benzene would be more resistant to bacterial attack since bacteria degrade benzene oxidatively. Still, slow degradation of benzene would probably occur in the absence of oxygen since some bacteria may be able to carry out hydroxylation reactions substituting H_2O for molecular oxygen.[78] The anaerobic metabolism of aromatics, however, remains little studied.[77] In addition the presence of benzene in combination with other aromatics (e.g., toluene, xylene) might result in unpredictable effects on the microbial population in a given environment.

Once present in the environment, aromatic compounds such as benzene may or may not undergo substitution reactions of various types, not involving microorganisms. The presence of nitro, amino or sulfonic acid groups or halogens on the ring will almost always render benzene and related compounds more microbiologically resistant.[77,79]

Background Concentrations. The presence of benzene in groundwater has been used to indicate subterranean petroleum or gas condensates. Groundwater from petroleum-free areas or strate contain less than 0.1% benzene. Groundwater near petroleum deposits may contain as much as 5.3% benzene[80] or 2.4% benzene homologs.[81] Sawicki[82] estimates that the "average" urban atmosphere contains 1×10^5 µg benzene/1,000 m^3, although an average of 0.015 ppm with a high of 0.057 ppm has been reported in Los Angeles air.[57] Parkinson[83] measured benzene in airborne vapor concentrations around retail gasoline filling stations and found benzene at concentrations less than 5 ppm, but they may reach as high as 7 ppm.[57] Gasoline may contain up to 5% benzene.[57]

Animals

Mammals. Domestic livestock has been treated topically with benzene to eliminate infestations of screwworm larvae.[84] Parman[84] observed no toxic effect on sheep and goats where the wool was completely saturated on all parts of the body with benzene. In cases where infestations occurred in the mouth, they were treated with 2 to 5 cc benzene, and special precautions were taken to prevent ingestion. No reports of detrimental effects to the animals were observed in these and over 3,000 similar treatments for worm infestation in cattle, sheep, goats, hogs and chickens.

Birds. Extracts of pigeon muscle exposed to benzene exhibited an increase in the creatine content of the muscle for several hours.[85] The significance of this event is not explained, although creatine and phosphocreatine are associated with the manufacture of ATP consumed during muscle contraction.

Fish. The acute toxicity of benzene to fishes is summarized in Table A-3. Results from the various researchers are relatively consistent as shown by the 96-hour LC_{50} which ranged from 9.58 to 40-45 mg/l. These data show benzene to be relatively toxic to fishes. An exception is the value (386.0 mg/l) presented by Wallen et al.[86] for the mosquito fish, Gambusia affinis, which is an order of magnitude greater than all other reported values. Pickering and Henderson[87] found no significant difference in the 96-hour LC_{50}'s for fathead minnows, Pimephales promelas, in soft and hard water. Their data also indicate that most of the toxicity of benzene is exhibited within 24 hours. However, since all of their tests were static bioassays, this may actually be a reflection of the degradation or evaporation of benzene in the test water, and subsequent decrease in the toxicity of the test solution. The toxicity of benzene to Pacific herring, Clupea pallasi, and northern anchovy, Engraulis mordax, eggs and larvae was at the same level as that observed for adults.[88]

TABLE A-3. SUMMARY OF BENZENE TOXICITY TO FISHES

Species	LC_{50} (mg/l) 24 hr	48 hr	96 hr	Test Conditions[a]	Reference
Pimephales promelas (fathead minnow)	35.36	35.08	33.47	pH 7.5; DO 7.8; hardness 20; static bioassay	87
Pimephales promelas (fathead minnow)	34.42	32.00	32.00	pH 7.5; DO 7.8; hardness 360; static bioassay	87
Lepomis macrochirus (bluegill sunfish)	22.49	22.49	22.49	pH 7.5; DO 7.8; hardness 20; static bioassay	87
Carassius auratus (goldfish)	34.42	34.42	34.42	pH 7.5; DO 7.8; hardness 20; static bioassay	87
Lebistes reticulatus (guppy)	36.60	36.60	36.60	pH 7.5; DO 7.8; hardness 20; static bioassay	87
Morone saxatilus (striped bass)	--	--	9.58	Temp 17.4°C; Salinity 29 ppt; flow-through bioassay	89
Lepomis macrochirus (bluegill sunfish)	20.00	20.00	20.00	pH 6.9-7.5; hardness 84.0-163.0; static bioassay	90
Gambusia affinis (mosquito fish)	395.00	395.00	386.00	Temp 20-22°C; pH 8.1-84; static bioassay	86
Clupea pallasi[b] (Pacific herring)	--	--	40-45	Temp 10-17°C; Salinity 24 ppt; static bioassay	88
Clupea pallasi[c] (Pacific herring)	--	20.25	--	Temp 12.9°C; Salinity 24 ppt; pH 7.9; DO 7.0; static bioassay	88
Engraulis mordax[d] (Northern anchovy)	--	20.25	--	Temp 12.9°C; Salinity 24 ppt; pH 7.9; DO 7.0; static bioassay	88

a. Dissolved oxygen (DO) and hardness in mg/l.
b. Eggs at hatching.
c. Two-day-old larvae.
d. One-day-old larvae.

Brocksen and Bailey[91] exposed juvenile chinook salmon Oncorhynchus tshawytscha, and striped bass, Morone saxatilis, to sublethal concentrations of benzene (5.0 and 10.0 ppm) for periods ranging from 1 to 96 hours. Results showed increases in respiratory rates up to 115% above that of controls after exposure periods of 24 hours for striped bass and 48 hours for chinook salmon. Fish exposed to a benzene concentration of 10.0 ppm for periods longer than 48 hours exhibited a narcosis that caused a decrease in the respiratory rate. This effect was shown to be reversible when fish were placed in fresh water and kept for periods greater than 6 days.

Brown et al.[92] have identified benzene as one of numerous compounds present in the Fox River, Wisconsin, which had a higher incidence of tumors in fishes than those from a reference area in Ontario, Canada (4.38% vs. 1.03%). Actual concentrations of benzene were not given.

Funasaka et al.[93] showed that fishes living in a river with high hydrocarbon concentrations had an offensive odor. In fish with offensive odor the concentrations of toluene, benzene, and xylene in the muscle were 0.25, 0.23, and 0.02 ppm, respectively. Those values roughly corresponded to relative levels of these compounds found in the river. Some hydroxylation of benzene to phenol reportedly occurs in the kidney and muscle tissue.[91] Phenol and phenolic compounds have been shown to cause fish flesh tainting.[94] For additional information see Appendix B on Toluene.

Reptiles. No information available.

Amphibians. No information available.

Invertebrates. Gavaudan and Nichon[95] report that in vitro samples of the dorsal longitudinal muscle of the earthworm Allolobophora terrestris longa respond to very small amounts of benzene. The reaction is characterized by a marked increase in tone and amplitude of rhythmic contractions.

Benzene is toxic to insects. Moore[96] reported that 10-20 mg was toxic to house flies, Musca domestica, when the insects were exposed in 1-liter flasks for periods of 185 to 427 minutes. Benzene produced 100% mortality in 3-day-old house flies when applied to the ventral side of the abdomen at 0.001 ml/fly.[97] Parman[84] reported that larval screwworms, Cochliomyia macellaria, became inactive in about 40 seconds when treated topically with benzene. When benzene was applied to wounds in cattle, screwworm larvae survived for 30 to 40 minutes, but were killed quickly when the wounds were dried before treatment.[84] Benzene caused 100% mortality in 2 hours when sprayed on 3rd-instar larvae of the bottle fly, Lucilia sericata.[98] Benzene is a repellent to both the screwworm and the house fly.[99] Benzene is toxic to the American cockroach, Periplaneta americana;[100] a toxic dose was not reported, but the authors stated that the lethal time

at the most effective dose was 0.5 that of DDT used as a standard. Benzene vapors are toxic to the grain weevil, Calandra granaria, with an LD_{50} (actually an LC_{50}) of 210 mg/liter reported by Ferguson and Pirie.[101] Benzene prevents or terminated diapause in eggs of the grasshopper, Melanoplus differentialis.[102] Benzene is toxic to the head louse, Pediculus humanus capitis, when applied to human subjects, apparently through ovicidal action.[103]

Microorganisms. The only potential problems associated with the effects of benzene on microorganisms would occur when environmental conditions became anaerobic and/or when benzene concentrations reached a microbially toxic level. High concentrations of aromatics can be toxic even to organisms which can completely metabolize them. Phenol is perhaps best known in this respect. Young and Mitchell[104] have shown that certain motile marine bacteria exhibit negative chemotaxis toward benzene concentrations greater than 0.2%, even though this level is non-lethal to the microbes. Mitchell et al.[105] have discussed the ecological implications of chemotaxis by microbes in nature. They feel that low sublethal levels of aromatics in the environment may totally inhibit the normal chemotactic response of microorganisms towards nutrient sources. If so, the abilities of microorganisms to detect nutrients in nature would be impaired. Benzene is effective in the control of Peronospora tabacina in tobacco seedbeds at a daily dose of 4-5 liters/100 m^2.[106] Barash[107] noticed that 200 mg/l benzene produced a marked reduction in the CH_4 fermentation rate of sewage sludge. Fifty mg/l was considered a level safe to the microorganisms responsible for the CH_4 evolution. Gibson[108] was able to grow Pseudomonas putida, strain A8, in benzene when benzene was introduced in the vapor phase. Saturating levels of benzene were toxic to P. putida.

Plants

Phytotoxic and Metabolic Effects. Benzene has a number of effects on plants ranging from changes in growth and metabolism to death.

Currier[109] investigated the phytotoxic effect of benzene vapors at three concentrations for 1/4 to 4 hours on young barley plants. Toxic response (percent injury) increased with length of exposure time and concentration. Benzene vapors caused 100% injury 24 hours after treatment with 6.4×10^{-4} M benzene for 1/2 hour. Lower concentrations, 2.2×10^{-4} M and 3.2×10^{-4} M, with the same exposure time, produced only 25% and 85% injury, respectively. Plants exposed to 6.4×10^{-4}, for only 1/4 hour suffered 40% injury. Measurements of the plants 1-4 weeks following exposure indicate that some degree of recovery is possible in the plants exposed to sublethal treatments. These results are presented in Table A-4. Pinckard et al.[110] too found that at atmospheric pressure, benzene vapor or

TABLE A-4. PERCENT INJURY TO BARLEY AS A FUNCTION OF BENZENE VAPOR CONCENTRATION, LENGTH OF EXPOSURE AND TIME AFTER TREATMENT

Time After Treatment	Length of Exposure (hrs) 1/4	1/2	1	2	4
	Benzene at 2.2×10^{-4} M/Liter of Air				
24 hours	-	-	-	-	-
1 week	2	25	25	25	25
2 weeks	2	30	25	25	25
4 weeks	0	0	0	0	0
	Benzene at 3.2×10^{-4} M/Liter of Air				
24 hours	60	85	98	98	-
1 week	60	85	98	100	-
2 weeks	50	75	98	100	-
4 weeks	30	50	100	100	-
	Benzene at 6.4×10^{-4} M/Liter of Air				
24 hours	40	100	-	-	-
1 week	-	100	-	-	-
2 weeks	40	100	-	-	-
4 weeks	25	100	-	-	-

spray at concentrations above 2% injures tobacco seedlings if the foliage is wet. Dry seedlings withstand concentrations greater than 3%. Currier[109] demonstrated the difference in susceptibility among species. Tomato, barley and carrot plants were exposed to benzene vapors at 3.2×10^{-4} M. Carrots, like other Umbelliferae, were far less susceptible to benzene than were either of the other species at short exposure times. For example, carrots were not damaged by exposure to 3.2×10^{-4} M benzene vapors for 1/4 hour, although barley and tomato plants suffered 60 and 80% injury, respectively. As exposure time increased, no significant difference was seen among species. All three plant species showed the ability to recover from sublethal exposure.

Benzene can elicit in plants a positive, negative or neutral growth response, depending on the concentration and plant species. Currier[109] treated tomato cuttings with 0, 1/100 saturated, 1/10 saturated and saturated solutions of benzene. Earlier and more vigorous rooting was produced in the 1/100 and 1/10 saturated solutions. The saturated solution killed the stem. Moore et al.[111] and Meites[112] demonstrated the stimulatory effect of benzene at low concentrations to maize seedlings and white lupine, respectively. Meites[112] suggested that the mechanism for growth stimulation involves the breakdown of protein by benzene, causing the release of tryptophan from which growth hormones, principally indole acetic acid, are produced. Growth inhibition was induced in Triticum aestivum leaves by a 0.1-0.15% solution of benzene[113] while 1000 mg/l benzene do not inhibit growth of tomato seedlings.[114]

Other effects of benzene involve interference with metabolism and cell division. Gavaudan et al.[113] found that a 0.2% benzene solution completely inhibited chlorophyll synthesis in etiolated Triticum aestivum leaves exposed to light. Mitosis was stopped by a 0.1% solution. Carpentier and Pacault[115] applied 0.005-0.1 M solution to young roots of Allium cepa and observed complete mitoclasis, i.e. mitotic disruption, while Meites[116] noticed an inhibition of mitosis in garlic rootlets treated with a nearly saturated aqueous benzene solution. Benzene also initiates the oxidation of glutathione by a lipoxidase enzyme in ungerminated pea seeds. Normally, oxidation occurs only in germinated seeds, but benzene is believed to change the fatty acid substrate, thus making it more accessible to the enzyme.[117] Benzene increased the Vitamin B content in the endosperm of treated brown rice[118] and reduced a functional disorder in stored apples called scald.[119]

Several researchers have proposed a possible mechanism for the phytotoxic effects of benzene but, unfortunately, no recent work has been done on the subject. The studies available recognize benzene as a good lipid solvent. Meites[116] found that benzene acts as a delipidizing agent in a histological study of the chondriomes of root meristems. Pinckard et al.[110] postulated that the toxic action of benzene involved the dissolution of the lipid portion of the plasma membrane and, as a result, disturbance of selective permeability. Currier,[109] too, comes to this conclusion, but

offers an interesting explanation for the transport of benzene through the hydrophilic cell wall and into the plasma membrane. Since benzene is far more toxic when administered in solution with water than paraffin oil, and far more soluble in oil than water, Currier explains the toxicity of benzene on the basis of partition coefficients. Benzene leaves the administered aqueous solution, and becomes more easily dissolved in the lipid-rich plasma membrane. Benzene applied in oil solutions, however, is less likely to become dissolved in water in the cell wall, enters the cell in lower concentrations, and hence is less toxic when administered in this manner.

The gross signs of benzene poisoning include darkening of the leaf tip, loss of turgor, and bleaching of chlorophyll in bright sunlight.[109]

Bioaccumulation. At high concentrations of benzene, quick killing of plant tissue is a likely result with little or no translocation and/or accumulation. At sublethal concentrations, and in a steady state condition, the fatty substances in the leaf (and probably other plant parts) would have greater amounts of benzene than the aqueous phases. But, there is no evidence to suggest that benzene is bioaccumulated in any quantity.

Translocation and Degradation. Benzene is apparently translocated and degraded by plants. Durmishidze and Ugrekhelidze[120] administered radioactive benzene to the roots of tea, laurel, grape and corn plants. They noticed that benzene was assimilated by the roots and decomposed to radioactive CO_2 in all parts of the plant, including the fruit. Later, they conducted a similar study[121] with tea plants but detected in all parts of the plant radioactive intermediates such as fumaric acid, succinic acid and malonic acid which are apparently formed directly from muconic acid. The proposed sequence of benzene metabolism in plants is as follows:

benzene ⟶ phenol ⟶ pyrocatechol ⟶ o-benzoquinone ⟶ muconic acid

Their later experiments with tea and grape leaf homogenates support this conclusion.[122] Tkhelidze[123] showed that grape berries metabolize radioactive benzene and emit radioactive CO_2. Apparently the berries contain an enzyme system capable of breaking the benzene ring into aliphatic compounds. Avocado fruit also have the ability to absorb benzene vapors and convert benzene to CO_2 and other unidentified compounds.[124]

Food Chain

There is no information on the transport or impact of benzene on the food chain. No prediction can be made of the danger which benzene-contaminated plants pose to humans or herbivores. However, it is unlikely that any substantial amount of bioaccumulation occurs. Fish, and probably other aquatic organisms, absorb benzene from contaminated

water and store it in muscle and liver tissue. There is no information on benzene storage by mammals, but xylene, a close chemical relative of benzene, can be stored in the meat of pigs. However, xylene is cleared soon after dietary exposure is terminated. Meat or fish tainted with even small amounts of benzene assumes an odor noxious to humans, and probably other consumers. For this reason, the danger of exposure to benzene through food seems limited.

EXISTING STANDARDS

The NIOSH recommended standard for a 40-hour workweek is 10 ppm (32 mg/m^3) as a time-weighted average (TWA) with a ceiling concentration of 25 ppm (80 mg/m^3).[20]

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APPENDIX B

TOLUENE

I. TIVE NAMES

Toluol; methylbenzene; benzene, methyl; phenylmethane; methacide

PHYSICAL AND CHEMICAL PROPERTIES[1,2]

Basic Physico-Chemical Information

CAS Reg. No. 108-88-3

Toxic Substances List: XS52500

Wiswesser Line Notation: 1R

Molecular formula: C_7H_8

Molecular weight: 92.13

Conversion factors (air, 20°C): 1 ppm = 3.77 mg m^3; 1 mg m^3 = 0.265 ppm

Freezing point: -94.991°C

boiling point: 110.623°C

Density: 0.86231 g/ml at 25°C

Refractive index: n_D = 1.49413 at 25°C

Vapor pressure:[2] $\log_{10} P = 6.95334 - [1343.943 / (219.377 + t)]$

where P is vapor pressure in mm of mercury and t is temperature in °C. (Thus, the vapor pressure at 26.04°C is 30 mm.)

Solubility in water: 0.0566 weight percent at 20.1°C.[3] Other values were close to this.[1,4,5]

Solubility in organic solvents: Miscible in alcohols and ethers and soluble in most organic solvents

Partition coefficient between vapor and water: 5.14 (20.06°C),[3,5] where K_p = Conc. in liq./ Conc. in vapor.

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Partition coefficients between the aqueous phase and immiscible organic solvent layers have been determined by a few investigators.[6,7] For example,[7] values of K_d (K_d = Conc. in organic phase/Conc. in aqueous phase) are 490 for Octanol and 708 for n-heptane. The odor threshold for toluene is 2.14 ppm.[8]

Sources of spectral data are given in Table B-1. Toluene is fairly stable in atmospheric and very stable in aqueous and soil environments, and is affected by other inorganic, organic and biochemicals only under extreme conditions, or through enzymatic action.

TABLE B-1. SOURCES OF SPECTRAL DATA FOR TOLUENE

Type of Spectra	Sources of Spectral Collections	Reference Collection Number	Ref
Infrared	Aldrich Library of IR Spectra	15-500-4	27
Ultraviolet	Sadtler Research Laboratories, Inc. 3316 Spring Garden St., Philadelphia, PA	SAD-155	28
Nuclear Magnetic Resonance	Varian NMR Data Collections	VAR-157	29
	Aldrich Library of NMR Data	--	30
Mass	John Wiley & Sons, Inc., 605 3rd Ave., New York, NY	Wiley-189	28

Photochemistry

Alkylbenzenes are photoisomerized to valence isomers in low yields, the particular products depending on the conditions.[9] Oxygen atoms produced by the photolysis of ozone and nitrogen dioxide can react with aromatic hydrocarbons.[10] Thus, toluene released to the atmosphere might disappear by oxidation.[10]

Manufacture and Uses

Toluene is produced industrially by fractionation of light oil of coke oven gas, carburetted water gas, coal tar, and aromatic fractions from petroleum cracking, and hydroforming. It is used largely as a basic raw material in the manufacture of materials such as dyestuffs, polymers, fibers, detergents, and synthetic chemicals. It is used also as an antiknocking ingredient in motor fuels, and as a solvent in chemical processing, paints and varnishes, dry cleaning, degreasing, and extraction.[1]

Biochemical Properties

The methyl group of toluene is readily oxidized by enzymes in mammals to form benzoic acid, which is eliminated in the form of hippuric acid in the urine.[11-13] Small amounts of benzyl alcohol are also formed, intermediate to the formation of benzoic acid. However, the hydroxylation of toluene to *o*- and *p*-cresol takes place only to 0.4-1.1% of the total. Therefore, unlike benzene, only very small quantities of epoxides must be formed by monooxygenases, i.e., on the way to forming cresols. The mechanisms involved in such oxidations are summarized by Jerina et al.[14,15] Toluene absorption can be estimated by monitoring the benzoic acid in urine by GLC analysis.[11]

Toluene can also be oxidized to *o*- and *p*-cresols (through epoxides) by the monooxygenases of the fungus Cunninghamella bainieri,[16] and to the dihydrodiols by the dioxygenases of Pseudomonas sp., through the formation of dioxy compounds.[17]

ANALYTICAL METHODS

Although spectrophotometry may be used for detection, identification and estimation of toluene, the standard GLC method with hydrogen flame-ionization detection can be used efficiently down to 15-25 ppb with pre-calibrated equipment. Details of this method, using automatic, semi-automatic or manual procedures, are available in many original articles and reviews.[11,18-26] The estimation can be made either directly from the air, water or fluid samples, or from samples of toluene preconcentrated by adsorption on activated charcoal contained in a tube.[22]

MAMMALIAN TOXICOLOGY

Toluene is the subject of a document published by NIOSH in 1973 and entitled, "Criteria for a Recommended Standard for Occupational Exposure to Toluene."[11] The following paragraph appears in the introduction to that document:

"For many years, toxicity to the blood and blood forming organs has been attributed to toluene, primarily because of the close structural similarity which exists between toluene and benzene and the established myelotoxicity of benzene. Toluene has been contaminated frequently with benzene. Current scientific evidence obtained from human and animal studies indicates that chemical alkylation of the benzene ring structure, such as exists with toluene (methyl benzene), results in a loss of the myelotoxic activity. Benzene appears to be unique among the monocyclic aromatic hydrocarbons in its myelotoxic properties; therefore, the major problem of toluene toxicity concerns its narcotic effects on workers by causing symptoms and signs such as muscular weakness, incoordination, and mental confusion which may pose a risk to both the worker and others."

Current production methods result in a relatively pure product (98-100%) and impurities, other than benzene, that may be present appear to contribute very little to the toxicity of toluene. Because of the presence of benzene in commercial grades of toluene in earlier years, the toxicology published prior to 1961 is not reliable. Even more recent publications may be suspect unless the purity of the toluene used has been specified and the amount of benzene present was less than 0.1%.

Human Exposures

Because of the above history, accounts of human exposure in the workplace are, for the most part, suspect. The most reliable data have been developed from laboratory experimental exposures on a small number of subjects. At 200 ppm in the air for 7-8 hours, transitory mild throat and eye irritation and slight exhilaration were noted. These signs and symptoms become more exaggerated until at 800 ppm metallic taste, transitory headaches, extreme lassitude, dim vision, verbosity, inebriation and slight nausea were reported.[11]

Repeated dermal exposure to toluene results in skin damage characterized by cracking and dermatitis. These changes are thought to be the consequence of a loss of lipid components of the skin through the solvent properties of toluene. Also, toluene is absorbed slowly through the skin as determined in experiments on human subjects. The amount of undiluted toluene absorbed varied from 14 to 23 mg/cm^2/hour. Absorption from aqueous solutions is slower. Toluene vapor in concentrations above 200 ppm and direct splashes of toluene in the eye has resulted in slight to severe eye irritation with subsequent complete recovery.[11]

Habituation to toluene has been seen in a few instances in painters and "glue sniffers." Such individuals absorb considerable amounts of toluene, even up to the point of unconsciousness. In most cases such exposure resulted in no pathological changes.[11] However, one case, in which renal and liver damage, as revealed by serum creatinine, blood urea (renal function), alkaline phosphatase, and serum bilirubin (liver function), has been reported recently.[31]

Of the toluene that is systemically absorbed, about 20% is excreted in the breath and the remainder is mostly converted to benzoic acid and excreted via the urine as hippuric acid. Humans and other animals appear to metabolize toluene similarly. In the rat, small quantities of three additional metabolites have been reported: benzyl alcohol, *o*-cresol, and *p*-cresol.[12] It appears that other species qualitatively metabolize toluene in the same fashion, although data are lacking for the cresols and benzyl alcohol.[11] These same metabolites probably occur in the urine of humans, but it might be difficult to determine that toluene was the precursor.

Experimental Animals

The most recent available oral LD_{50} for toluene in male rats (150-200 g) is 5.58 g/kg.[32] Other LD_{50} values for non-fasted, Sprague-Dawley rats reported since 1970 are: 14-day-old mixed sex, 3.0 ml/kg; young male adults (80-160 g), 6.4 ml/kg; and mature male adults (300-470 g), 7.4 ml/kg. Converting these to weight figures the values are 2.6, 5.54, and 6.41 g/kg, respectively.[33]

In a study to determine the effect of differences in protein in the diet on the toxicity of toluene, toluene dissolved in oil was injected subcutaneously into rats every other day for 24 weeks, at the rate of 1 ml/kg. Semi-synthetic diets, normal protein diets and half-normal protein diets were fed to the animals. On the normal diet, the only groups to be considered here, body weight gain, hematocrit, and hemoglobin were not markedly reduced over the experimental period.[34] While the study was reported in 1968, the purity of the toluene was not stated.

Little attention has been paid to the potential carcinogenic, mutagenic, or teratogenic action of toluene, at least using toluene of known purity. However, from experiments that have been conducted using pure toluene, from human experience, and from knowledge of the metabolic end products of toluene, it can reasonably be expected that toluene in low repeated doses would have no such potential.

ENVIRONMENTAL CONSIDERATIONS

Behavior in Soil and Water

Transport. Very little information is available on the transport of toluene in the soil. However, it is known that toluene can be degraded by microbes.[35] Toluene's adsorptive properties on clays and other soil particles are not known. Based on the data available, if toluene were present in low concentrations, it would be expected to volatilize or be degraded within a short period of time. The transport of high concentrations of toluene in the soil is impossible to predict without further information.

Animals

Mammals. Young dogs have been treated orally with a combination of toluene (600 mg) and dichlorophen (500 mg) for the treatment of the larvae and adults of Ancylostoma caninun.[36] No report of adverse effects to the puppies was made, but this treatment did eliminate the worms.

Birds. No information available.

Fish. The acute toxicity of toluene to fishes is summarized in Table B-2.

These data show toluene to be moderately toxic. The 96-hour LC_{50} from acute bioassays ranged from 22.80 ppm for the goldfish, Carassius auratus,[39] to 59.30 mg/l for the guppy, Lebistes reticulatus.[37] Pickering and Henderson[37] also showed that hardness had little effect on the toxicity of toluene to fathead minnows, Pimephales promelas, and that most of the toxicity occurred within the first 24 hours. Brennian et al.,[39] however, showed the toxicity to progressively increase (LC_{50}'s decrease) with time (Table B-2). Pickering and Henderson's values are higher, apparently because they used static bioassays instead of flow-through bioassays. Most of the original toluene was probably lost by evaporation during the first 24 hours. Brennian's 96-hour LC_{50}'s were lower than those of Pickering and Henderson, again probably as a result of differences in test methods. The values reported by Wallen et al.,[38] are two orders of magnitude greater than all other reported. This difference in magnitude of LC_{50} values was not explained.

The only long-term study of the toxicity of toluene was also conducted by Brennian et al.[39] They determined the 720-hour (30 days) LC_{50} for goldfish to be 14.58 ppm with 95% confidence limits of 10.73 to 19.96. This is significantly less than their 96-hour LC_{50} of 22.30 ppm.

Brown et al.,[40] has identified toluene as one of numerous compounds present in the Fox River, Wisconsin, which appeared to be associated with a higher incidence of tumors in fishes than those from a reference area in Canada (4.38% vs. 1.03%). Concentrations of toluene were not given.

Funasaka et al.,[41] showed that fishes living in a river with high hydrocarbon concentrations had an offensive odor. In fish with offensive odor the concentrations of toluene, benzene, and xylene in the muscle were 0.25, 0.23, and 0.02 ppm, respectively. These values roughly corresponded to relative levels of these compounds found in the river. Ogata and Miyake[42] showed that eels kept in an industrial water from a petroleum plant for a week at 5°C, and after being boiled, gave off a

TABLE 5-2. SUMMARY OF TOLUENE TOXICITY TO FISHES

Species	LC_{50} (mg/l) 24 hr	48 hr	96 hr	Test Conditions[a]	Reference
Pimephales promelas (fathead minnow)	46.31	46.31	34.27	pH 7.5; DO 7.8; hardness 20; static bioassay	37
Pimephales promelas (fathead minnow)	56.00	56.00	42.33	pH 7.5; DO 7.8; hardness 360; static bioassay	37
Lepomis macrochirus (bluegill sunfish)	24.00	24.00	24.00	pH 7.5; DO 7.8; hardness 20; static bioassay	37
Carassius auratus (goldfish)	57.68	57.68	57.68	pH 7.5; DO 7.8; hardness 20; static bioassay	37
Lebistes reticulatus (guppy)	62.81	60.95	59.30	pH 7.5; DO 7.8; hardness 20; static bioassay	37
Gambusia affinis (mosquito fish)	1,340	1,260	1,180	Temp 20-22°C; pH 7.5-8.5; static bioassay	38
Carassius auratus[b] (goldfish)	41.59	27.62	22.80	pH 7.0; temp 17-19°C; DO 7.0; hardness 80; flow-through bioassay	39

a. Dissolved oxygen (DO) and hardness in mg/l.
b. Values in ml/l.

bad odor. They confirmed the presence of benzene, toluene, and *m*-, *o*-, and *p*-xylene in muscle and liver of the eels. They also identified toluene to be responsible for imparting the odor to the fish. They concluded that toluene dissolved in seawater is absorbed by eels directly and infiltrates into the muscle perhaps through blood from the branchia, and it cannot be removed by boiling or cooking. In additional experiments they mixed solutions of benzene, toluene, *m*-, or *p*-xylene and *p*-xylene each in equal concentrations with seawater containing eels once a day for 5 days. The eels muscle and liver contained *p*-xylene, *o*-xylene, toluene, and benzene in a decreasing order of quantity. The seawater contained about the same concentration of benzene, toluene, and xylene, and the ratio of concentration (μg/g wet weight) of muscle to that (ppm) of seawater is of the order of *o*-xylene (1.9) > *m*-xylene (1.6) > toluene (0.8) > benzene (0.2) (Table B-3). This suggests that these compounds do not significantly bioaccumulate; however, low tissue levels of toluene do cause fish flesh tainting.

TABLE B-3. MEAN CONCENTRATION OF BENZENE, TOLUENE, AND XYLENE ISOMERS IN MUSCLES AND LIVERS OF EELS KEPT IN WATER CONTAINING ADDED AROMATIC HYDROCARBONS (μg/g body weight)[42]

	Benzene	Toluene	*o*-Xylene	*m*-Xylene	*p*-Xylene
Muscle	4.7	12.4	25.1	21.7	30.1
Liver	1.5	4.8	6.1	5.2	26.6

Reptiles. No information available.

Amphibians. No information available.

Invertebrates. Ancylostoma caninun, hookworm, was eliminated in experimentally infected puppies by treatment with a combination of toluene and dichlorophen.[36] An oral dose of 600 mg toluene and 500 mg dichlorophen was 98% effective against fourth-stage larvae and immature worms in the experimentally infected puppies. Toluene is also used as an anthelmintic for cats.[43] Vincent[44] showed that very low concentrations of toluene induce rhythmic contractions of leech muscle.

Toluene is toxic to insects. Moore[45] reported that 5-10 mg was toxic to house flies, Musca domestica, when the insects were exposed in 1-liter flasks for periods ranging from 256 to 600 minutes. Toluene produced 100% mortality in 3-day-old house flies when applied to the venter of the abdomen at 0.0004 and 0.001 ml/fly.[46] Toluene is converted

to benzoic acid when incubated with house fly abdomens or the fat bodies of locusts, Schistocerca gregaria.[47] Toluene vapors are toxic to the grain weevil, Calandra granaria, with an LD_{50} (actually an LC_{50}) of 96 mg/liter reported by Ferguson and Pirie.[48] Toluene prevents or terminates egg diapause in the grasshopper, Melanoplus differentialis.[49]

Microorganisms. Little information was retrieved concerning the toxicity of toluene towards microorganisms. Barash[50] noticed that 20 mg/l toluene produced a temporary increase in the rate of CH_4 evolution of sewage sludge deposits, and considered it a safe level. A sharp reduction in the rate of CH_4 fermentation was observed following the addition of 200 mg/l toluene. Saturating levels of toluene are toxic to Pseudomonas putida, strain AB, but rapid growth on toluene was observed when toluene was introduced in the vapor phase.[51] Young and Mitchell[52] reported that certain motile marine bacteria exhibit negative chemotaxis toward toluene concentrations greater than 0.1% (as compared to 0.2% for benzene). A 0.6% level has been shown to completely inhibit the normal chemotactic response of motile marine bacteria.[53]

Bacterial attack on toluene proceeds in a fashion similar to attack on benzene. Toluene is hydroxylated prior to ring cleavage.[54] Toluene is converted by this mechanism to 3-methyl catechol. Methyl substituents may also be affected by bacterial action, but may remain intact during hydroxylation.[54] After hydroxylation the methyl groups may be oxidized to carboxylic acid groups. Carboxyls may be removed prior to ring cleavage, but may remain intact on the ring.

Plants

Phytotoxic and Metabolic Effects. Toluene has been shown to have several effects on plants, depending on the concentration. At low levels, toluene stimulates growth and interferes with the functioning of certain enzyme systems, while at higher concentrations it can kill the plant.

The toxic effects of toluene on plants have been studied by Currier,[55] who exposed young barley plants to three concentrations of toluene vapor for different lengths of time. This study showed that increasing the concentration of vapors from 0.69×10^{-4} M to 4.9×10^{-4} M in air produced an increase in the percent injury to the barley plants. With plants exposed to low concentrations, doubling the exposure time also greatly increased the percent injury. Measurements taken from 1 to 4 weeks following the exposure showed that, to some extent, recovery of the plants was possible after exposure to any of the concentrations for short periods of time. Table B-4 summarizes the results.

TABLE B-4. PERCENT INJURY TO BARLEY AS A FUNCTION OF TOLUENE VAPOR CONCENTRATION, LENGTH OF EXPOSURE AND TIME AFTER TREATMENT[55]

Time after Treatment	Length of Exposure (hrs) 1/8	1/4	1/2	1	2
	Toluene at 0.69×10^{-4} M/Liter of Air				
24 hours	-	2	50	40	50
1 week	-	2	25	25	25
2 weeks	-	0	25	25	25
4 weeks	-	0	25	15	15
	Toluene at 1.3×10^{-4} M/Liter of Air				
24 hours	-	70	80	98	100
1 week	-	50	75	98	100
2 weeks	-	50	60	98	100
4 weeks	-	60	50	98	100
	Toluene at 4.9×10^{-4} M/Liter of Air				
24 hours	95	98	100	-	-
1 week	85	98	100	-	-
2 weeks	75	100	100	-	-
4 weeks	60	100	100	-	-

In tests using three plant species, Currier[55] observed that carrot plants were far less susceptible to toluene vapors at the same exposure times than were tomato or barley plants. Carrot plants suffered no injury after exposure to 1.3×10^{-4} M toluene for 1/4 hour (Table B-5), while the same treatment produced 85% injury in tomato plants (Table B-5) and 70% injury in barley (Table B-4). Little species difference in toxic response was noticed at longer exposure times, and all species had the ability to partially recover from sublethal doses. Currier believes that resistence to pure aromatic hydrocarbons is a characteristic of many members of the Umbelliferae, including carrot, parsnip, celery, dill and parsley.

TABLE B-5. PERCENT INJURY TO TOMATO AND CARROT PLANTS AS A FUNCTION OF TIME AFTER TREATMENT AND LENGTH OF EXPOSURE TO TOLUENE VAPORS AT 1.3×10^{-4} M/LITER OF AIR[55]

Time after Treatment	Length of Exposure (hrs) 1/4	1/2	1	2
	Tomato			
24 hours	85	95	98	100
1 week	75	85	90	100
2 weeks	60	75	85	100
4 weeks	50	60	75	100
	Carrot			
24 hours	0	2	90	98
1 week	0	50	85	95
2 weeks	0	60	75	90
4 weeks	0	50	75	75

Signs of toxicity include a darkening of the tips of leaves, loss of turgor, and bleaching of chlorophyll in bright sunlight.[55] Damage to the plasma membrane is a toxic action of toluene. Miwa et al.,[56] for example, noticed that toluene vapors damaged the semipermeability of the protoplasma of sweet potatoes, causing a hardened outer covering. Pringshein[57] also noticed that toluene affected the intake of water by seeds of Lupinus, Zea and Pisum. Toluene appears to enter the plant readily, probably through the stomata and cuticle.[55] Absorption appears to depend on such factors as the lipid make-up of the cuticle and plasma membrane, surface tension and rate of vaporization.[55]

Although the toxic mechanism of toluene is not fully understood, several researchers have proposed a possible mechanism for the toxicity of benzene, a close chemical relative of toluene, based on its ability to dissolve lipids. Meites,[58] for example, found that benzene acts as a delipidizing agent in a histological study of the chondriomes of root meristems. Pinkard et al.,[59] postulated that the toxic action of benzene involved the dissolution of the lipid portion of the plasma membrane and, as a result, disturbance of selective permeability. Currier,[55] too, comes to this conclusion, but offers an interesting explanation for the transport of benzene through the hydrophilic cell wall and into the plasma membrane. Since benzene is far more toxic when administered in aqueous

solution than in paraffin oil, and far more soluble in oil t[illegible]r. Currier explains the toxicity of benzene on the basis of parti coefficients. Benzene leaves the administered aqueous solution and becomes more easily dissolved in the lipid-rich plasma membrane. Benzene applied in oil solutions, however, is less likely to become dissolved in water in the cell wall, enters the cell in lower concentrations, and hence is less toxic when administered in this manner. Toluene toxicity probably has a mechanism similar to that of benzene.

Currier[55] noticed that low concentrations of toluene can enhance growth. Tomato cuttings were placed in Hoagland's solution with 0, 1/100 saturated, 1/10 saturated, and saturated amounts of toluene. Rooting was more extensive and produced earlier in cuttings in 1/10 and 1/100 saturated solutions. Saturated solutions of toluene not only inhibited root formation, but killed the stem.

Another effect of toluene is the initiation of the oxidation of glutathione by a lipoxidase enzyme in ungerminated pea seeds. This is thought to be due to a change in the fatty acid substrate induced by toluene, thus making it more accessible to the enzyme. Normally, oxidation of glutathione occurs only in germinated seeds.[60]

Bioaccumulation. At high concentrations of toluene quick killing of plant tissue is a likely result, with little or no translocation and/or accumulation. At sublethal concentrations and in a steady state condition the fatty substances in the leaf (and probably other plant parts) would have greater amounts of hydrocarbon than the aqueous phase. But, there is no evidence to suggest that toluene is bioaccumulated in any quantity.

Degradation. Currier,[55] in 1951, reported that toluene was not metabolized by higher plants. More recently, however, Tkhelidze[61] found that ^{14}C-toluene was metabolized in grape berries during germination, growth, and maturation. An enzyme system is apparently responsible for degrading the benzene ring and transforming aromatic to aliphatic compounds.[61] Jansen and Olson[62] observed the metabolism of toluene to CO_2 in avocado fruit.

Food Chain

The dearth of information available on toluene's impact on the environment makes predictions of its effects on the food chain difficult. No prediction can be made of the danger which toluene-contaminated plants pose to humans or herbivores. Fish apparently can store certain amounts of toluene in muscle and liver tissue; the compound is not removed by cooking.[41,42] The noxious odor of toluene-contaminated fish would limit human and possibly piscivore exposure to toluene through food and possibly protect the fish from predation.

EXISTING STANDARDS

NIOSH has recommended that the time-weighted average (TWA) exposure to toluene for a 40-hour workweek be limited to 100 ppm (377 mg/m^3). The maximum exposure concentration to prevent the narcotic effects of toluene should be limited to 200 ppm (754 mg/m^3). The odor threshold is reported by NIOSH to be 40 ppm (150 mg/m^3).[63]

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APPENDIX C

XYLENES

ALTERNATIVE NAMES

The three xylene isomers:

1. *o*-Xylene; *o*-xylol; 1,2-dimethylbenzene; benzene, 1,2-dimethyl
2. *m*-Xylene; *m*-xylol; 1,3-dimethylbenzene; benzene, 1,3-dimethyl
3. *p*-Xylene; *p*-xylol; 1,4-dimethylbenzene; benzene, 1,4-dimethyl

PHYSICAL AND CHEMICAL PROPERTIES[1,2]

	o-Xylene	*m*-Xylene	*p*-Xylene
CAS Reg. No.	00095476	000108383	000106423
Toxic Substances List:	ZE24500	ZE22750	ZE26250
Wiswesser Line Notation:	1RB	1RC	1RD
Molecular formula:	$C_6H_4(CH_3)_2$	$C_6H_4(CH_3)_2$	$C_6H_4(CH_3)_2$
Molecular weight:	106.16	106.16	106.16
Freezing point:	-25.182°C	-47.872°C	13.263°C
Boiling point:	144.411°C	139.103°C	138.351°C
Density: (20°C)	0.8802	0.8642	0.8610
Refractive index: n_D^{20}	1.50545	1.49722	1.49582

Vapor pressure:[1] $\log_{10} P = A - B/(C + t)$ where P is vapor pressure in mm of mercury and t is temperature in °C.
For *o*-Xylene, A = 7.00289; B = 1477.519, C = 214.024;
For *m*-Xylene, A = 7.00659, B = 1460.498, C = 214.889;
For *p*-Xylene, A = 6.99099, B = 1453.840, C = 215.367

Conversion factors (air, 25°C): 1 ppm = 4.34 mg m^{-3}; 1 mg m^{-3} = 0.230 ppm

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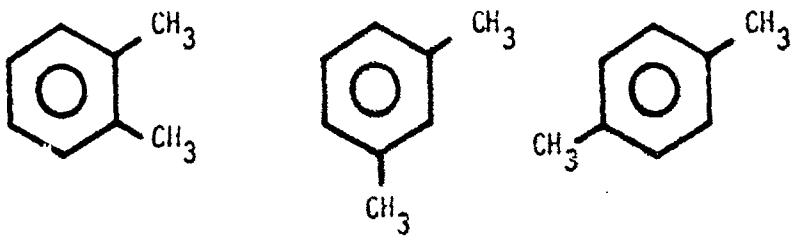
Structural formula:



o-Xylene *m*-Xylene *p*-Xylene

Solubility in water:[3] *o*-Xylene = 0.0228 g/100 ml water at 22°C

m-Xylene = 0.0187 g/100 ml water at 22°C

p-Xylene = 0.0191 g/100 ml water at 22°C

Sources of spectral data are given in Table C-1.

Xylenes are miscible with ethers and alcohols in all proportions and are soluble in many other organic solvents.[2]

The partition coefficients for the xylenes for octanol/water and n-heptane/water have been listed by Leo Hansch and Elkins.[8] They lie in the vicinity of 10^3.

Xylenes are not very susceptible to reaction with environmental chemicals in the absence of drastic conditions or enzymes.

Photochemistry

Alkylbenzenes are photoisomerized to valence isomers in low yields, the particular products depending on the conditions.[9] Oxygen atoms produced by the photolysis of ozone and nitrogen dioxide can react with aromatic hydrocarbons.[10] Thus, xylenes released to the atmosphere might disappear by oxidation.[10]

Manufacture and Uses of Xylenes

The sources of xylene are light oil from coke oven gas or coal tar, and petroleum naphtha from either selected prime cuts or catalytically formed distillates. The proportion of the *ortho*, *meta*, and *para* isomers in mixed xylenes, which are the normal commercial products, vary with the production source. The proportions are approximately 10-25% *ortho*, 45-70% *meta* and 6-15% *para*. Impurities include toluene, trimethylbenzene, phenol, thiophene, pyridine, and non-aromatic

TABLE C-1. SOURCES OF SPECTRAL DATA FOR XYLENES

Type of Spectra	Sources of Spectral Collections	Reference Collection Number	Reference
Infrared	Aldrich Library of IR Data	*o*-Xylene = x-104-0 *m*-Xylene = 13,490-2 *p*-Xylene = 13,444-9	4
Ultraviolet	Sadtler Research Laboratories, Inc. 3316 Spring Garden St., Philadelphia, PA	*o*-Xylene = SAD-7 *m*-Xylene = SAD-317 *p*-Xylene = SAD-609	5
Nuclear Magnetic Resonance	Varian NMR Data Collections	*o*-Xylene = VAR-201 *m*-Xylene = VAR-202 *p*-Xylene = VAR-203	6
	Aldrich Library of NMR Data	--	7
Mass	John Wiley & Sons, Inc. 605 3rd Ave., New York, NY	*o*-Xylene = Wiley-322 *m*-Xylene = Wiley-323 *p*-Xylene = Wiley-326	5

hydrocarbons.[11] The separation can be carried out by fractional crystallization of *p*-xylene at -3.9°C and fractional distillation of *m*-xylene, leaving *o*-xylene in the still. The xylenes are used for making phthalic anhydride, isophthalic acid, and terephthalic acid for the paint and fiber industries, and for making xylidenes as antiknocking ingredients for motor fuels. Either commercial or other blends of xylenes are used as industrial, cleaning, degreasing, processing, extracting, or thinning solvents.[2]

Biochemical Properties

The xylenes are generally susceptible to metabolic oxidation on one of the methyl substituents, after which they form corresponding hippuric acids, and are eliminated through the urinary tract. However, very small percentages are known to undergo epoxidation by monooxygenases isolated from mammalian livers, subsequent transformation to dihydrodiols, and finally conversion to xylenols.[11,12] The microbiological oxidation of *p*- and *m*-xylenes by Pseudomonas putida 35/D (by dioxygenases) is known to occur, with consequent formation of cis-dihydrodiols. The stereochemistry of this transformation is discussed by Gibson et al.[13]

The oxidation of the methyl substituent in xylenes, (*para* and *meta*) is also caused by Pseudomonas Pxy and Pseudomonas Pxy-40. *m*-Xylene is transformed to *m*-tolualdehyde, and *p*-xylene, to *p*-tolualdehyde. But 3-methylcatechol and 3-methylsalicylic acid are produced by the action of Pseudomonas Pxy-82 on *m*-xylene. The pathways of these transformations are discussed by Gibson et al.[14]

The above information on metabolism (and the effect of microbial enzymes) confirms the fact that the formation of the reactive epoxide takes place to a very small extent only; the major reaction is the oxidation of the methyl side chain through normal modes of oxidation and dehydrogenation.

ANALYTICAL METHODS

Xylenes can be detected, identified and estimated by spectral methods, but the small quantities that generally occur in the environment would usually be measured by G.C with hydrogen flame ionization detection, either directly or as preconcentrated samples. Excellent original articles and reviews are available in the literature.[15-27]

MAMMALIAN TOXICOLOGY

Xylene is the subject of a review document published in 1975 by NIOSH entitled "Criteria for a Recommended Standard for Occupational Exposure to Xylene."[11] The following paragraph has been excerpted from its introduction:

"For many years, myelotoxicity (toxicity to the blood and blood-forming organs) has been attributed to xylene, primarily because of the close structural similarity which exists between xylene and benzene and the established effects of benzene on the blood and blood-forming organs. Xylene has been contaminated frequently with benzene. Current scientific evidence obtained from human and animal studies indicates that alkylation of the benzene ring, such as exists with xylene (dimethylbenzene), results in a loss of these blood effects. Benzene appears to be unique among the monocyclic aromatic hydrocarbons in these myelotoxic properties. Therefore, the major problem of xylene toxicity concerns its narcotic effects on workers, causing symptoms and signs such as muscular weakness, incorrdination, and mental confusion which may pose a risk to both the worker and others."

Human Exposures

Since earlier experimental work and accidental exposures were with a solvent of unknown composition, any signs and symptoms attributed to xylene may have been substantially incorrect. However, in a study published in 1975,[28] xylene, of the composition shown in Table C-2, was tested on volunteers for 15 minute exposure periods. Observations made are shown in Table C-3 and indicate an odor threshold of the order of 1 ppm (4.5 mg/m^3) in air. Xylene used as a vehicle for paint apparently was responsible for the death of one painter and the anesthesia, for durations of 15 and 18 hours, respectively, of two painters, as a result of these individuals working in a confined space where the xylene concentration was estimated to be about 10,000 ppm. The two survivors showed an elevated blood urea and reduced creatinine clearance in one and elevated serum transaminase in both, with ultimate recovery to normal.[29]

Xylene is irritating to the skin and mucous membranes in humans and when applied to the skin produces a curious dilitation of the superficial blood vessels under the skin which persists for several minutes.[11,30]

The isomers of xylene are converted by humans to the corresponding toluic (methylbenzoic) acid, which is then conjugated with glycine in the case of the *meta* and *para* isomers and excreted in the urine. The *ortho* isomer is also oxidized to the corresponding toluic acid but probably is conjugated differently before excretion in the urine, if one can extrapolate from experiments in animals.[11,31] It has been suggested that the excretion of methylhippuric acid in the urine could be used to monitor exposure to xylene.[31]

TABLE C-2. COMPOSITION OF MIXED XYLENES TESTED ON HUMAN VOLUNTEERS

Components[a]	Volume Percent[b]
Non-aromatics	0.07
Toluene	0.14
Ethylbenzene	19.27
o-Xylene	7.63
m-Xylene	65.01
p-Xylene	7.84
Higher aromatics	0.04
Total	100.00

a. Note the absence of benzene.
b. Determined by gas chromatography.

TABLE C-3. ODOR DETECTION AND SENSORY THRESHOLD FOR MIXED XYLENES TESTED ON HUMAN SUBJECTS[28]

Odor Threshold				
Metered concentration, mg/liter	0.0	0.001	0.01	0.1
Corrected concentration, mg/liter	0.0	0.0006	0.006	0.06
Corrected concentration, ppm	0.0	0.14	1.4	14
No. of positive responses in two trials combined (6 volunteers per trial; 12 total)	0	0	8	12

Conclusion: The odor threshold lies between 0.0006 and 0.006 mg/liter with the most probable concentration being 0.0045 mg/liter or 1.0 ppm

Sensory Thresholds				
Measured concentration, mg/liter	0.46	1.0	2.0	3.0
Measured concentration, ppm	110	230	460	690
Exposure order	2nd	1st	3rd	4th
Number of volunteers	6	7	6	6
Number detecting odor	6	7	6	6
Number olfactory fatigue	3	3	3	0
Number throat irritation	1	0	1	2
Number eye irritation	0	1	4	4
Number with tears	0	1	1	2
Number reporting dizziness	0	1	1	4
Number tasting "something"	0	1	0	3
Sensory Thresholds				
Number with effects 1 hr after exposure	0	0	0	0

Conclusion: A concentration of 0.46 mg/liter (110 ppm) should not be objectionable to most people

Experimental Animals

Figures shown in Table C-4 have been assembled from the Registry of Toxic Effects of Chemical Substances.[32]

TABLE C-4. ACUTE TOXICITY OF XYLENES TO THE RAT

Route	LD_{50} (mg/kg)			
	Mixed Xylenes	*o*-Xylene	*m*-Xylene	*p*-Xylene
Oral	4,300	5,000	5,000	5,000
Intraperitoneal	2,000	1,500	2,000	2,000
Subcutaneous	-	2,500	5,000	5,000

These figures indicate little difference in the toxicity of the individual isomers of xylene or of mixtures of isomers, with the exception of the parenteral routes for *o*-xylene. By these routes *o*-xylene appears slightly more toxic.

The one modern study available using mixed xylenes of known composition[28] utilized a dosage schedule of 6 hours per day, 5 days per week, for 13 weeks by inhalation. The measured exposure levels were 3.5, 2.0, 0.77, and 0.0 mg/liter of air for both rats and dogs. No lesions that could be ascribed with certainty to the xylene exposure were seen at 3 and 7 week interim sacrifices or at the 13 week termination. Parameters in the rats consisted of red cell counts, white cell counts, hematocrit, hemoglobin, and differential white cell counts as well as blood chemistry determinations for blood urea nitrogen, glutamic oxaloacetic and pyruvic transaminases and alkaline phosphatase. The same parameters plus blood glucose and bilirubin were followed in the dogs.

Scattered reports of possible teratogenic or mutagenic activity may be found in abstracts of the Eastern European literature. However, since the purity of the xylene is not described, these observations are of limited value.

In laboratory animals, as in humans, about 25% of an absorbed dose is excreted unchanged via the lungs, with the remainder metabolized to the corresponding toluic acids which are then conjugated, mostly with glycine, and excreted in the urine.[11] Small amounts of dimethylphenols

from the corresponding xylenes have been found in the urine of rats. *p*-Xylene gives rise to 2,5-dimethylphenol; *m*-xylene to 2,4-dimethylphenol; and *o*-xylene to 3,4-dimethylphenol, 2,3-dimethylphenol, and 2-methylbenzyl alcohol.[33] The two dimethyl phenols from the *o*-xylene are compatible with an arene oxide intermediate which would also explain why the *ortho* isomer is somewhat more toxic than the *meta* and *para*.

ENVIRONMENTAL CONSIDERATIONS

Behavior in Soil and Water

Transport. Very little information is available concerning the transport of xylene in the soil, but some predictions can be made based on the sparse information present. Xylene can be microbially degraded.[34] It is probable that low concentrations of xylene are degraded or volatilize within a short period of time. The pathway for high concentrations of xylene in the soil is impossible to forecast without further information.

Animals

Mammals. Pigs were fed for 55 days on a basal diet which included fish meal containing 0.17% and 1.17% xylene. Xylene had no effect on weight gain, but it depressed the normal increase in the albumin - globulin ratio. Meat from the pigs fed the diet containing 1.17% xylene was unsuitable for human consumption, presumably because of odor, when the pigs were slaughtered shortly after feeding. When the pigs were removed from the xylene treatment for 2 days, and then slaughtered, the meat was satisfactory.[35]

Birds. Jellinek (cited in 36) exposed chick embryos to an unstated concentration of xylene vapor for 60 to 240 minutes. As the length of exposure increased, so did the incidence of malformation and mortality.

Fish. The acute toxicity of xylene to fishes is summarized in Table C-5. These data show xylene to be moderately toxic. The 96-hour LC_{50} ranged from 16.94 ppm in flow-through tests for the goldfish, Carassius auratus,[37] to 36.81 mg/l in static tests.[38] Values for other species were intermediate. Pickering and Henderson[38] also showed that hardness had little effect on the toxicity of xylene to fathead minnows, Pimephales promelas, and that all of the toxic effects were observed within the first 25 hours. Brennian et al.,[37] however, showed the toxicity to progressively increase (LC_{50}'s decrease) with time.

Since Pickering and Henderson[38] used static bioassay, most of the xylene was probably lost due to evaporation within the first 24 hours. This is reflected in comparisons of the 24-, 48-, and 96-hour LC_{50} determined by Pickering and Henderson[38] and those determined by Brennian et al.[37]

TABLE C-5. SUMMARY OF XYLENE TOXICITY TO FISHES

Species	LC_{50} (mg/l) 24 hr	48 hr	96 hr	Test Conditions[a]	Reference
Pimephales promelas (fathead minnow)	28.77	27.71	26.70	pH 7.5; DO 7.8; hardness 20; static bioassay	38
Pimephales promelas (fathead minnow)	28.77	28.77	28.77	pH 7.5; DO 7.8; hardness 360; static bioassay	38
Leopomis macrochirus (bluegill sunfish)	24.00	24.00	20.87	pH 7.5; DO 7.8; hardness 20; static bioassay	38
Carassius auratus (goldfish)	36.81	36.81	36.81	pH 7.5; DO 7.8; hardness 20; static bioassay	38
Lebistes reticulatus (guppy)	34.73	34.73	34.73	pH 7.5; DO 7.8; hardness 20; static bioassay	38
Carassius auratus[b] (goldfish)	30.55	25.10	16.94	pH 7.0; Temp 17-19°C; DO 7.0; hardness 80; flow-through bioassay	37

a. Dissolved oxygen (DO) and hardness in mg/l.
b. Values in ml/l.

Funasaka et al.[39] showed that fishes living in a river with high hydrocarbon concentrations had an offensive odor. In fish with offensive odor the concentrations of toluene, benzene, and xylene in the muscle were 0.25, 0.23, and 0.02 ppm, respectively. The values roughly corresponded to relative levels of the compounds found in the river. They were unable to determine what compounds caused the odor. Folmar[40] conducted avoidance studies on rainbow trout fry (Salmo gairdnari) with xylene. He found that the fry were significantly attracted to 0.01 mg/l and avoided 0.1 mg/l xylene. Although the avoidance occurs at a non-toxic level, this could have a significant impact on the trout by influencing their selection of habitat. For additional information see Appendix B on Toluene.

Reptiles. No information available.

Amphibians. No information available.

Invertebrates. Stover[41] reports that Dowfume H-940 (74% xylene and 26% by weight of bromomethane) appears to act as a nematicide as well as a fungicide.

Xylene is toxic to insects. Moore[42] reported that 5-10 mg was lethal to house flies, Musca domestica, when the insects were exposed in 1-liter flasks for periods ranging from 95 to 911 minutes. Xylene produced 100% mortality when applied to the venter of the abdomen of 3-day-old house flies (0.002 ml/fly).[43] Xylene is also toxic to the American cockroach, Periplaneta americana, in studies reported by Munson and Yeager.[44] Although these authors did not report the toxic dose for xylene, they stated that the lethal time at the most effective dose was 0.12 that of DDT used as a standard. Xylene vapors are toxic to the grain weevil, Calandra granaria, with LD_{50} (actually LC_{50}) of 31 mg/liter (*o*-xylene) and 48 mg/liter (*p*-xylene) reported by Ferguson and Pirie.[45] Xylene has also been reported to prevent or terminate diapause in eggs of the grasshopper, Melanoplus differantialis.[46]

Microorganisms. Xylene is toxic to some microorganisms. In concentrations of 500-1000 ppm, xylene eliminated root rot, Phymatotrichum omnivorum, on plants, but it also eliminated the host plant.[47]

Xylenes are often microbiologically hydroxylated to xylenols as a preliminary step towards ring cleavage.[48] Hydroxylation, as with benzene and toluene, is followed by ring cleavage utilizing molecular oxygen. The methyl substituents of xylene may or may not be oxidized prior to ring cleavage.

The potential effects of anaerobic conditions and/or high concentrations of toluene or xylene on microorganisms are essentially the same as discussed for benzene. Gibson[49] reports that Nocardia spp. are able to

utilize xylene as a food source when it is introduced as a vapor. However, saturating levels of xylene are toxic.

Plants

Phytotoxic and Metabolic Effects. The phytotoxicity of xylene appears to depend on the type of application, plant part treated, and plant species. Xylene was applied by spray to alfalfa, tomatoes, dwarf corn, squash, potatoes and beans at concentrations of 370, 740 and 1480 ppm by volume. This experiment was conducted to determine the safety of using xylene-contaminated water, from aquatic weed control programs, for irrigation. Neither visible injury to the crops nor reduced crop yield or growth rate was produced.[50] Klostermeyer and Skotland,[51] however, report that xylene in unmentioned concentrations is toxic to hops and remains phytotoxic up to 3 years in light sandy soil. Chinaberry, maple and elm sustained severe injury when their roots were treated with 500-1000 ppm xylene for the control of root rot, Phymatotrichum omnivorum.[47]

Currier[52] measured the percent injury in young barley plants exposed to xylene vapors. By using three concentrations, and exposure times from 1/8 to 4 hours, Currier showed that percent injury increased with increased concentration and increased exposure time (Table C-6). There was no damage to plants exposed to 0.20×10^{-4} M xylene for 1 hour, while 2.4×10^{-4} M for the same time period produced 100% injury. All plants, except those exposed to lethal treatments, recovered at least partially after 1-4 weeks. In an experiment to determine the comparative susceptibility of three plant species to xylene vapors, Currier[52] found that carrot plants were injured far less than tomato or barley plants. At 0.46×10^{-4} M xylene for 1 hour, for example, barley plants suffered 95% injury after 24 hours, while tomatoes showed 85% injury and carrots 2% injury after the same period. All plant species were able to recover to some extent following sublethal treatments. Members of the family Umbelliferae, including carrot, celery and parsley, appear to have a high tolerance for pure aromatic hydrocarbons, according to Currier.[52]

The signs of toxicity of xylene are similar to those of other aromatic hydrocarbons, i.e., loss of turgor, darkening of leaf tip and bleaching of chlorophyll in bright sunlight.[52] Xylene is considered to be less toxic than benzene or toluene,[52] but the toxic mechanism for all three is probably the same. Currier[52] believes that xylene, like toluene and benzene, disrupts the lipid-rich plasma membrane since it is a good fat solvent. Although the hydrophilic cell wall acts as a partial barrier to xylene, since xylene is only sparingly soluble in water, the lipophilic plasma membrane readily absorbs xylene. Other lipophilic organelles, chloroplasts, and mitochondria are probably also damaged by xylene.

TABLE C-6. PERCENT INJURY TO BARLEY AS A FUNCTION OF XYLENE VAPOR CONCENTRATION, LENGTH OF EXPOSURE AND TIME AFTER TREATMENT

Time of Treatment	Length of Exposure (hrs) 1/8	1/4	1/2	1	2	4
	Xylene at 0.20×10^{-4} M/Liter of Air					
24 Hours	-	0	0	0	2	80
1 Week	-	0	0	0	2	75
2 Weeks	-	0	0	0	2	50
4 Weeks	-	0	0	0	0	10
	Xylene at 0.46×10^{-4} M/Liter of Air					
24 Hours	-	75	85	95	98	-
1 Week	-	60	60	75	90	-
2 Weeks	-	25	40	70	85	-
4 Weeks	-	25	25	50	75	-
	Xylene at 2.4×10^{-4} M/Liter of Air					
24 Hours	75	95	98	100	-	-
1 Week	60	85	95	100	-	-
2 Weeks	40	80	95	100	-	-
4 Weeks	30	75	90	100	-	-

Other effects of xylene on plants include changes in growth, translocation, germination, dormancy and longevity of cut flowers. Currier[52] placed tomato cuttings in Hoagland's solution with 0, 1/100 saturated, 1/10 saturated, and saturated amounts of xylene. In the 1/100 and 1/10 saturated solutions the tomato cuttings rooted earlier and more extensively than controls. Fully-saturated solutions killed the stem. Moore et al.,[53] observed a similar effect of xylene on the primary roots of maize seedlings. Vitamin B_1 in the endosperm of brown rice increased with treatment of xylene.[54] When pollen grains of Chrysanthemum pacificum and Lilium longiflorium were soaked in xylene for varying periods of time, they became temporarily dormant but recovered their initial activity when removed from the solvent.[55] The germination of seeds of beans, squash, radish, oat and lettuce was retarded for 6 to 30 days by xylene, in concentrations of approximately 500-2000 qt/acre, alone or in combination with other chemicals.[56] Dormant potato tubers, on the other hand, germinated sooner after soaking in xylene or treatment with the vapor for 16-24 hours.[57] Cotton, however, was planted on soil treated 16 days earlier, with xylene, and no effects were noted.[47] Hosticka et al.,[58] observed that xylene interfered with the translocation of 2,4-D applied to castor bean leaves.[58] At concentrations of 100-500 ppm, xylene prolonged the life of many cut flowers including aster, antirrhinum, chrysanthemum, and acrolelinium, although some bleaching of the petals was observed.[59]

Bioaccumulation. At high concentrations of xylene, quick killing of plant tissue is a likely result with little or no translocation and/or accumulation. At sublethal concentrations and in a steady state condition the fatty substances in the leaf (and probably other plant parts) would have greater amounts of xylene than the aqueous phase. But, there is no evidence to suggest that xylene is bioaccumulated in any quantity.

Degradation. No information was retrieved on the metabolism of xylene in plants. Toluene and benzene, close chemical relatives of xylene, are metabolized to CO_2 by the fruit of avocado and grape plants.[60,61]

Aquatic Vegetation. Frank et al.,[62] observed the response of three species of water-weed (Elodea canadensis, Potamogeton nodosus) exposed to xylene + 2% nonionic emulsifier weekly for 4 weeks. They found nearly 100% kill at 100 ppm and observed no effects at 5 ppm. Thirty minute contact and subsequent removal at 300 and 600 ppm also resulted in significant effects.

Food Chain

There is no information available on the transport of xylene through the food chain. Data on the action of xylene in plant cells is too inconclusive to permit a prediction of the dangers of humans or herbivores exposed to xylene-contaminated plants. Xylene or its metabolites appears to accumulate in fish and mammals during sublethal exposure but

is eliminated in mammals shortly after removal of the xylene source. The noxious odor of animals exposed to xylene might deter predators from consuming contaminated prey and limit man's exposure to food contaminated with moderate amounts of xylene.

EXISTING STANDARDS

In order to prevent a narcotic effect and to guard against irritation of mucous membranes, a limit for xylene as a time-weighted average (TWA) of 100 ppm has been recommended by NIOSH.[11] Limit values recommended in various parts of the world are shown in Table C-7.

TABLE C-7. XYLENE EXPOSURE LIMITS

Country	mg/m^3	ppm
Bulgaria	100	23[a]
Czechoslovakia	200	46
(single exposure)	1,000	230
Finland	870	200
Germany (Federal Republic)	870	200
Hungary	50	12[a]
Japan	670	150
Poland	100	23[a]
Rumania	200	46[a]
USSR	50	12[a]
Yugoslavia	400	100

a. Equivalent values calculated by NIOSH.

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APPENDIX D

p-CHLOROPHENYL METHYL SULFIDE
p-CHLOROPHENYL METHYL SULFOXIDE
p-CHLOROPHENYL METHYL SULFONE

ALTERNATIVE NAMES

p-Chlorophenyl methyl sulfide: Benzene, 1-chloro-4-(methylthio)-; chlorophenyl methyl sulfide (*para*); sulfide, 4-chlorophenyl methyl.

p-Chlorophenyl methyl sulfoxide: Benzene, 1-chloro-4-(methylsulfinyl)-; chlorophenyl methyl sulfoxide (*para*); sulfoxide, 4-chlorophenyl methyl.

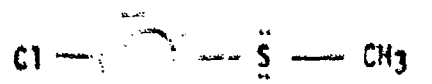
p-Chlorophenyl methyl sulfone: Benzene, 1-chloro-4-(methylsulfonyl)-; chlorophenyl methyl sulfone (*para*); sulfone, 4-chlorophenyl methyl.

PHYSICAL AND CHEMICAL PROPERTIES

Basic Physico-Chemical Information

Chemical Structures:

p-Chlorophenyl Methyl Sulfide



p-Chlorophenyl Methyl Sulfoxide

p-Chlorophenyl Methyl Sulfone

Physico-Chemical Properties:

The more important physical properties of the three compounds are presented in Table D-i.

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TABLE D-1. SELECTED PHYSICO-CHEMICAL PROPERTIES OF *p*-CHLOROPHENYL METHYL COMPOUNDS

Property	*p*-Chlorophenyl Methyl Sulfide	Sulfoxide	Sulfone
CAS Reg. No.	123-09-1	934-73-6	98-57-7
Molecular Formula	C_7H_7ClS	C_7H_7ClOS	$C_7H_7ClO_2S$
Molecular Weight	158.65	174.65	190.65
Melting Point (°C)	17-19°	37-39°[1] 46-48°[3] 47-48°[5] 47°[6]	99°[2] 96°[4] 92°[1] 97-98°[7] 97°[8] 96.5-98°[9] 98-99°[6]
Boiling Point[a]	44/.08[b,10] 73°/1.5mm[12] 73-75°/2mm[12] 87°/5mm[14] 104.5°/11mm[16] 108°/12mm[11] 108°/13mm[6] 107°/14mm[17] 112°/18mm[18] 118°/20mm[2] 118°/23mm[19] 220-223°/760mm[20] 224°/760mm[21]	106-108°/0.8mm[7] 131-132°/2.5mm[6] 135-136°/5mm[5] 142-144°/6mm[15]	141°/3mm[11]
Density	1.202 g/ml/(49°C)[2]	Not known	Not known
Refractive Index	n_D^{20}=1.5997[17]	Not known	Not known
Electric moment	1.83 Debye units[18]	Not known	Not known
Molar Magnetic Suscep.	97.3[22]	Not known	103.1[22]
pK_a of Conjugate Acid	Not known	-1.57[3]	Not known
Water Solubility[2]	"Insoluble"	Not known	"Slightly Soluble"

a. From these data the vapor pressure equation for the sulfide was calculated to be

$$\text{Log}_{10} P(\text{mm}) = 8.9322 - \frac{2984.1}{T(°K)}$$

b. Not included in equation.

Spectroscopy

The infrared and Raman spectra of *p*-chlorophenyl methyl sulfide were measured on liquid-state samples over a very wide frequency range, 5000 to 40 cm^{-1} (corresponding to 2-250 micrometers); complete vibrational assignments were made.[23] In view of the usual range of an infrared spectrometer, i.e., 4000 to 670 cm^{-1} (corresponding to 2.5-15 micrometers),[24] not all the infrared vibrations would be significant for identification purposes. Among the more useful bands (units in cm^{-1}) are the following;[23] CH_3-S stretching, 719 (weak); CH_3 rocking; 957 (medium) and 969 (strong); antisymmetric methyl bending 1427 (very strong) and 1437 (strong); symmetric methyl bending 1320 (medium), strong and very strong aromatic stretching bands appear at 1476, 1389, 1112, 1096, 1011 and 811 cm^{-1}.[23] The 1096 cm^{-1} band has been attributed to - SCH_3 stretching;[11] this is elsewhere designated as the 1100 cm^{-1} asymmetric C-S stretching frequency.[12,25] A stretching frequency characteristic of the methyl group was reported at 2933 cm^{-1} in carbon tetrachloride.[26] A_1 vibration of theoretical interest is the C-C stretching band at 1576 cm^{-1}.[10]

The most analytically significant infrared absorptions (cm^{-1}) for *p*-chlorophenyl methyl sulfoxide are probably the following:[11] SO stretching, 1062 in CCl_4 (strong); especially -$S(O)CH_3$ stretching, 1089; symmetric methyl bending, 1305; antisymmetric methyl bending, 1415; methyl rocking, 950. The 1062 cm^{-1} band is shifted to 1050 cm^{-1} in chloroform.[27] A_1 vibration of theoretical interest is the C-C stretching band at 1574 cm^{-1}.[7]

For *p*-chlorophenyl methyl sulfone the following infrared bands (cm^{-1}) are characteristic: Asymmetric SO stretching, 1330;[7,11] symmetric SO stretching, 1158;[7,11] and especially - $S(O_2)CH_3$ stretching, 1087.[11] Other interesting absorptions[11] are: symmetric methyl bending, 1318; antisymmetric methyl bending, 1418; and methyl rocking, 965. A_1 vibration of theoretical interest is the C-C stretching band at 1584 cm^{-1}.[7]

p-Chlorophenyl methyl sulfide has ultraviolet absorption maxima at 214 nm (ϵ = 6,600)[16] and 261 nm (ϵ = 13,800)[16] or 260 nm (ϵ = 12,190)[26] with a shoulder at 292 nm (ϵ~ 1,000).[16] The corresponding sulfoxide exhibits maxima at 222 nm (ϵ = 10,700) and 240 nm (ϵ = 6,500) in ethanol, with a shoulder at 258 nm (ϵ = 2,900); the 240 nm peak shifts to 255 nm in cyclohexane (ϵ = 5900).[28] The ultraviolet spectrum for the sulfone was determined by Truce and Vriesen,[9] showing a maximum at 228 nm (ϵ~ 14,800) and a minimum at 210 nm.

Proton magnetic resonance chemical shifts are available for all protons in the three *p*-chlorophenyl methyl sulfur compounds (Table D-2). Moreover, ^{13}C nuclear magnetic resonance data have been obtained for all the carbons of these compounds.[29]

A mass spectrum has been determined for *p*-chlorophenyl methyl sulfone.[30]

Polarizations, refractions, dipole moments and molar Kerr constants have been measured in benzene and carbon tetrachloride for *p*-chlorophenyl methyl sulfide.[19]

TABLE D-2. PROTON MAGNETIC RESONANCE CHEMICAL SHIFTS FOR *p*-CHLOROPHENYL METHYL COMPOUNDS

p-Chlorophenyl Methyl Compound	Chemical Shift in Parts Per Million (δ)				
	Aromatic H				
	Ortho to S	Meta to S	Methyl H	Solvent	Ref.
Sulfide		7.18[a]	-	$CDCl_3$	31
		7.21[b]	-	$CDCl_3$	14
		7.15[c]	2.44	CCl_4	6
		-	2.335	CCl_4	32
		-	2.39	CCl_4	19
		-	1.94	C_6H_6	19
Sulfoxide	7.58	7.40	-	$CDCl_3$	31
		7.50[d]	2.59	CCl_4	6
Sulfone	7.86	7.54	-	$CDCl_3$	31
	7.94	7.55	3.03	$CDCl_3$	33
	7.88	7.52	2.93	CCl_4	6

a. Broad singlet for both types of aromatic proton.
b. AB quartet for the aromatic protons.
c. Attributed to meta position in the reference.
d. One value for both ortho and meta positions in the reference.

Manufacture, Origin and Laboratory Syntheses

The three sulfur compounds are intermediates in the manufacture of the herbicide Planavin.[34] They are currently available from the Parrish Chemical Company, Provo, Utah 84601.

p-Chlorophenyl methyl sulfide is manufactured by the methylation of *p*-chlorobenzenethiol with chloromethane in the presence of alkali.[34] Dimethyl sulfate can also be used for this methylation.[11,17,20] A Japanese patent describes a synthesis by pyrolysis of S-*p*-chlorophenyl-O-methyl dithiocarbonate.[13]

p-Chlorophenyl methyl sulfoxide is found in trace amounts in *p*-chlorophenyl methyl sulfone, an intermediate in the manufacture of Planavin.[34] The sulfoxide arises from the incomplete tungstate-catalyzed oxidation of the corresponding sulfide with hydrogen peroxide.[34,35] Another possible environmental source of the sulfoxide may be air oxidation of the sulfide after the latter's discharge. *p*-Chlorophenyl methyl sulfoxide is formed in good yield by the action of a variety of oxidants on the sulfide: Hydrogen peroxide in acetone or acetic acid;[15] sodium periodate in aqueous methanol;[11] acid-catalyzed hydrogen peroxide in aqueous ethanol;[5,36] 30% hydrogen peroxide at low temperature;[1,22] chromic anhydride at low temperature;[22] *t*-butyl hypochlorite in methanol at -80° to -70°;[3] bromine in aqueous methanol;[37] perbenzoic acid in chloroform at -5° to -0°.[27] Industrial production of the sulfoxide by oxidation of the sulfide with a mixture of oxygen and nitrogen dioxide appears to be efficient and clean.[35]

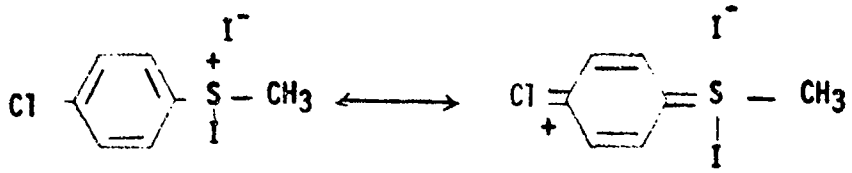
p-Chlorophenyl methyl sulfone may be formed from the sulfide or the sulfoxide by more vigorous oxidation than is used to make the sulfoxide, although the degrees of difference between sulfide and sulfoxide towards various oxidants under different conditions is not very well described. Miott, Modena and Sedea[37] say that oxidation of arylalkyl sulfoxides to sulfones is at least 50 times slower than oxidation of sulfide to sulfoxide by excess bromine in 2:1 methanol-water at 25°. In specific examples, the sulfide was oxidized to the sulfone by peroxyformic acid,[1] by 30% hydrogen peroxide in acetic acid at elevated temperature,[11,22] and by peroxybenzoic acid in aqueous dioxane.[5] The sulfone can be made from *p*-chloroaniline by the following route (where Ar = *p*-chlorophenyl):

$$ArNH_2 \longrightarrow ArN_2^+ \xrightarrow[Cu,\ H_2SO_4]{SO_2,\ H_2O} ArSO_2Na \xrightarrow[C_2H_5OH]{CH_3I} ArSO_2CH_3$$

The intermediate $ArSO_2Na$ may also be made by reduction of $ArSO_2Cl$ with sulfide.[38] It can also be made by Friedel-Crafts acylation of chlorobenzene with methanesulfonyl chloride and recrystallization of the product from aqueous ethanol.[39] The patent by Sanderson and Swift[35] describes formation of *p*-chlorophenyl sulfone, for Planavin production, from the sulfide or sulfoxide; the oxidation is conducted with mixed oxygen and nitrogen dioxide in sulfuric acid; the product contains some 3-nitro-4-chlorophenyl methyl sulfone, which is in any event desirable as an intermediate in Planavin syntnesis.

Chemical Reactivity

p-Chlorophenyl methyl sulfide forms a charge transfer complex with iodine in carbon tetrachloride with bands at 304 and 340 nm.[40] The yellow color, corresponding to the 457 nm band observed at higher sulfide concentrations, is attributed to iodosulfonium ion, two resonance forms of which are shown:



The relative ease of oxidation of sulfide to sulfoxide is apparent from specific instances referenced above. To the oxidants cited there may be added organic hydroperoxides,[41-43] even though these were not studied with *p*-chlorophenyl methyl sulfide. Numerous studies have been carried out on the kinetics and mechanisms of such reactions.[36,37,41,42,44] Strong acid catalyzes the oxidations by hydrogen peroxide[46] and by organic hydroperoxides,[41,42] though not by peroxyacids[45] or bromine.[37] In acidic medium, halogen oxidation, especially by iodine, is reversible.[37] There seems to be no direct evidence on the air oxidation of sulfides (or of sulfoxides), but the fact of nitrogen-dioxide catalysis[35] of oxidation of both the sulfide and sulfoxide by molecular oxygen argues convincingly for the thermodynamic feasibility of catalyzed air-oxidation processes. Furthermore, the ability of certain hydrocarbons to autoxidize, with formation of hydroperoxides (which oxidize sulfides, as shown above), suggests that mechanisms for organic co-oxidation of sulfides, if not catalysis of oxidation, may exist in the soil. If one adds potential biochemical pathways[1] to the foregoing, it becomes apparent that at least *p*-chlorophenyl methyl sulfide and *p*-chlorophenyl methyl sulfoxide should exhibit some interconvertibility in the environment.

The kinetics and mechanism of oxidation of phenyl methyl sulfoxide and a series of substituted-phenyl methyl sulfoxides by peroxybenzoic acid was studied at 25° in aqueous dioxane.[5] The parent substance showed a rate constant of $4.1 \times 10^{-2} M^{-1} sec^{-1}$, and the rate constants for the phenyl-substituted sulfoxides differed by a factor of less than 3. It is obvious that the rate of sulfide oxidation by peroxybenzoic acid would be many orders of magnitude greater.[45]

The chlorine of *p*-chlorophenyl methyl sulfoxide is somewhat activated by the sulfonyl group towards alkaline hydrolysis,[4,47] but not nearly so much as by a nitro group.[4] Drastic conditions are required for such reactions.

Biochemical Properties

Mouse liver and house fly microsomal preparations oxidize *p*-chlorophenyl methyl sulfide to the sulfoxide but not to the sulfone.[1] The sulfide inhibits sulfoxidation of the insecticide phorate by plant root extracts.[48]

ANALYTICAL METHODS

Water containing *p*-chlorophenyl methyl sulfide, *p*-chlorophenyl methyl sulfoxide and *p*-chlorophenyl methyl sulfone has been analyzed by the following gas chromatographic procedure:[49] The water sample is filtered through a 0.45-micron membrane filter. One hundred milliliters of this filtrate is extracted with two 5-ml portions of chloroform. The extract is adjusted to 10 ml, and a 10-microliter aliquot is injected onto a 1/4" x 6' column of 80/100 mesh Chromosorb W loaded with 10% FFAP. The injection port temperature of the Tracor MT-222 gas chromatograph is 225°C and the sulfur flame photometric detector temperature is 205°C. The column is maintained isothermal at 130° for 8 minutes, programmed at 10°C/mm up to 215°C, and held 14 min at 215°C. Elution times are 14.1 min for the sulfide, 21.5 min for the sulfoxide and 27.1 min for the sulfone. The detection limit is about 10 ppb. Extraction efficiencies were found to be 90%, 90% and 98%, respectively, for the three compounds.

The compounds were also identified by gas chromatograph/mass spectrometry on "silicone" columns temperature-programmed to 210° at the Environmental Protection Agency's Environmental Research Laboratory in Athens, GA.[50]

An isothermal gas chromatographic procedure was described by Nigg et al.[1]

MAMMALIAN TOXICOLOGY

Human Exposures

No information available.

Experimental Animals

The limited information available on the acute toxicity of these compounds is presented in Table D-3.

Severe skin reactions (edema with scale formation and brownish discoloration) were reported in rabbits treated dermally with the sulfoxide derivative.[51]

The sulfone has been reported to have anticonvulsant properties when tested on rats.[8]

TABLE D-3. ACUTE TOXICITY OF *p*-CHLOROPHENYL METHYL SULFIDE, SULFOXIDE, AND SULFONE

p-Chlorophenyl Methyl Compound	Oral LD50 Mouse, mg/kg[a]	Dermal LD50 Rabbit, mg/kg[a]
p-Chlorophenyl methyl sulfide	710 (480-1050)[b]	2000[c]
p-Chlorophenyl methyl sulfoxide	933 (852-1020)[b]	445 (200-990)[b]
p-Chlorophenyl methyl sulfone	570 (365-885)[b]	2000[c]
	2000[d]	

a. 95% confidence limits shown in parentheses.
b. Reference 51.
c. Reference 2.
d. Reference 8.

ENVIRONMENTAL CONSIDERATIONS

Behavior in Soil and Water

No information available.

Animals

No information available.

Plants

Very little information was retrieved concerning the phytotoxicity of these compounds. In one study[52] six grass and herb species were tested using three methods of application at two dosages. Foliage application of all three compounds produced no damage, but soil application and solution application of the compounds produced minor to extensive damage at the higher concentration used. A summary of the results of this study is presented in Table D-4.

p-Chlorophenyl methyl sulfide interferes with the enzyme system responsible for phorate sulfoxidation in root extracts of several plant species. Phorate, a plant systemic insecticide, is normally rapidly oxidized to phorate sulfoxide. But when phorate is present at a 1:10 ratio with p-chlorophenyl methyl sulfide, phorate sulfoxidation is significantly inhibited.[48]

TABLE D-4. EFFECT OF *p*-CHLOROPHENYL METHYL COMPOUNDS ON SIX PLANT SPECIES[52]

Soil Application (lbs/acre)				Foliage Application (lbs/acre)				Solution Application (ppm)			
Barnyardgrass *Echinochloa crusgalli*		Garden cress *Lepidium sativum*		Crabgrass *Digitaria sanguinalis*		Pigweed *Amaranthus* spp.		Downy Brome *Bromus tectorum*		Duckweed *Lemna minor*	
1	10	1	10	1	10	1	10	1	10	1	10
				p-Chlorophenyl methyl sulfide							
0	2	0	0	0	0	0	0	1	2	0	0
				p-Chlorophenyl methyl sulfoxide							
0	2	0	8	0	0	0	0	0	1	0	0
				p-Chlorophenyl methyl sulfone							
0	4	0	9	0	0	0	0	0	0	0	0

0 = no effect; 9 = complete kill.

Food Chain

No information available.

EXISTING STANDARDS

No information available.

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